IN THE UNITED STATES DISTRICT COURT

IN AND FOR THE DISTRICT OF DELAWARE

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AVENTIS PHARMACEUTICALS INC. and SANOFI-AVENTIS US LLC,	:	Civil Action
Plaintiffs,	:	
v.	:	
BARR LABORATORIES, INC.,	:	
Defendant.	:	No. 06-286-GMS

- - -

Wilmington, Delaware
Tuesday, May 20, 2008
9:00 a.m.

- - -

BEFORE: HONORABLE GREGORY M. SLEET, Chief Judge

APPEARANCES:

JOHN G. DAY, ESQ.
Ashby & Geddes
-and-
PAUL H. BERGHOFF, ESQ.,
JOSHUA R. RICH, ESQ.,
JEREMY E. NOE, ESQ.,
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JAMES HURST, ESQ.,
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Counsel for Defendant

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THE COURT: Good morning. Please be seated.

I understand that my chief deputy has made two calls. We are trying to do something about the heat.

You have some issues.

MR. RICH: We are still trying to work through them. We hope we will be able to work through the issue of the length of the deposition transcripts. The parties are working through an issue on the length of the deposition designations that defendant has made. Hopefully we will be able to work it out through the parties. But right now --

THE COURT: You are going to have to work it out through the parties because I will not involved myself with

it.

That's the beginning and the end of that.

What is the other issue?

MR. RICH: That is the only issue.

MR. BERGHOFF: Your Honor, Mr. Noe will handle our next witness.

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PLAINTIFF'S TESTIMONY

... DR. ROBERT Y. LOCHHEAD, having been placed under oath at 9:08 a.m. as a witness, was examined and testified as follows ....

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MR. NOE: May I approach, Your Honor?

THE COURT: You may.

(Documents passed forward.)

THE WITNESS: Thank you.

DIRECT EXAMINATION

BY MR. NOE:

Q. Good morning, Dr. Lochhead. Could you please state your full name for the court reporter?

A. Yes. My name is Robert Yates Lochhead.

Q. Dr. Lochhead, please describe your educational background?

A. I have a Bachelor of Science, Honors, in Pure Chemistry from the University of Strathclyde in Scotland; a

Ph.D. in Physical Chemistry; specifically, Molecular Rheology and Dielectric Relaxation of Polymer Solutions from the same university.

And I was a Fulbright Scholar as a post-doctoral fellow at Carnegie-Mellon University in the Department of Chemical Engineering.

MR. NOE: And as we were are going through some of these items off your CV, I'll ask Eric to call up Plaintiff's Trial Exhibit 359.

BY MR. NOE:

Q. Dr. Lochhead, how are you currently employed?

A. I'm currently employed as a Professor of Polymer Science; and I'm Chair and Director of the School of Polymers and High Performance Materials; and I'm also Director of Formulations Science at the Institute at the University of Southern Mississippi.

Q. Have you held any other positions at the University of Southern Mississippi?

A. Yes. I was formerly Dean of the College of Science and Technology.

Q. Did you hold any other faculty positions prior to the University of Southern Mississippi?

A. Yes, I was an adjunct faculty member in the School of Pharmacy at University of Cincinnati before I joined the University of Southern Mississippi and subsequently a few

years after I joined, University of Southern Mississippi.

Q. And, Dr. Lochhead, I'd like to remind you to please speak up for the court reporters' convenience.

As an adjunct professor at the University of Cincinnati School of Pharmacy, what kind of courses did you teach?

A. I taught a master's course in Formulation and Principles of Formulation. And I also was on student committees where I did, I oversaw student/graduate student research.

Q. What did you do prior to becoming a professor?

A. I headed up the hydrophilic polymer group at BF Goodrich where I was responsible for polymer synthesis and scaleup. I was also responsible for heading up the group that looked into the formulation of cosmetics and pharmaceuticals. That was part of my duties.

And prior to that, I worked for a research group in England where I helped formulators understand the physical processes of the behind existing formulations and also helped them to define the criteria required for developing new formulations.

Q. Have you done any consulting work for pharmaceutical companies?

A. Yes. For example, I've consulted with Johnson & Johnson on skin lotions and also vaginal lubricants. And

I've consulted with Proctor & Gamble where we designed cough syrup that had cough suppressant. It was designed to stay on the throat for a certain length of time and I helped them design the polymers into that product.

Q. Are you involved in any professional organizations that relate to your work?

A. Yes. I was President of the Association of Formulation Chemists. And that organization encompasses, it covers all aspects of formulation including pharmaceutical formulations. That organization is now matched with the American Chemical Society.

I'm also, I was also President of the Society of Cosmetic Chemists. And I'm currently Vice President Elect of the organization, and I will be President again in 2010.

I served on the committee for Scientific Affairs For the Society of Cosmetic Chemists. And I served on the International Nomenclature Committee of the Personal Care Products Council where I am responsible for naming product ingredients, polymer ingredients.

Q. Dr. Lockhead, how many publications do you have?

A. Oh, I have over 200 publications, dealing with polymers, rheology, formulation, and surfactants, and particles.

I also have 18 patents, I am the named inventor on 18 patents. Some of these patents are directed towards

the repair of tears in the retina, where we have designed polymer compositions that are thick so that they can be applied directly into the eye by the surgeon, and then they are thin, so they can be applied, and thicken up after application to repair a retinal tear.

I also have a patent for a bioadhesive polymer. That is a polymer that sticks to mucus, and in particular, this one was used for vaginal lubricants.

Q. **In your experience, what degree of overlap, if any, exists between cosmetic formulation and pharmaceutical formulation?**

A. **There is a large overlap between the two. In fact, people are transferred between cosmetics and pharmaceutical organizations.**

Q. **To your knowledge, do pharmaceutical companies hire scientists with cosmetic formulating skills?**

A. **Yes.**

Q. **Dr. Lockhead, how would you summarize your experience?**

A. **I have 30 years, more than 30 years experience in evaluating polymer rheology, evaluating rheology of polymer formulations and in testing formulations.**

I also have a thorough understanding of the concepts and physical principles of formulation, of thixotropy, rheology, and the testing of viscosity.

MR. NOE: Your Honor, plaintiffs offer at this time Dr. Lockhead as an expert in formulations and rheology.

MR. HURST: No objection.

THE COURT: The Doctor is accepted as an expert.

BY MR. NOE:

Q. **Dr. Lockhead, what were you asked to do in this litigation?**

A. **I was asked to review the patents in suit in light of the claim construction by the Court and by the parties involved.**

I was also asked to do some viscosity testing to discern whether Barr's proposed ANDA product met the specification limits, some of the specification limits in the claims in the patents in suit.

Q. **In addition to reviewing the patents in suit and the Court's claim construction order, did you review anything else?**

A. **I reviewed many documents, yes, many, many documents.**

Q. **Did you conduct viscosity testing of Barr's ANDA product?**

A. **Yes. I conducted the viscosity testing of Barr's ANDA product.**

Q. **Did you conduct viscosity of any other product?**

THE COURT: Had you finished your response?

THE WITNESS: Yes, I had finished.

THE COURT: Okay.

THE WITNESS: And I also looked into the viscosity of several other products, particularly for my opening part I tended to the viscosity specifications, and I tested viscosity of Nasacort AQ.

Q. **Did you prepare an expert report that describes the results of the viscosity testing that you just described?**

A. **Yes. I prepared an opening report. I wrote an opening report that described the results of my testing of Nasacort AQ and the viscosity testing of Barr's proposed ANDA product.**

Q. **Dr. Lockhead, are you familiar with the two patents at issue in this litigation?**

A. **Yes, I am. The patents describe thixotropic compositions. And the thixotropic compositions are defined as having a setting viscosity and a shear viscosity. Thixotropic compositions are compositions that are thick at rest and thin when sheared. And the setting viscosity and shear viscosity define the amount of thickness or thinness in these compositions.**

Q. **If we could call up 1.7.1, please.**

Dr. Lockhead, in Column 5 of the '573 patent, from Lines 18 to 24, how is the setting viscosity described as being measured?

A. **Well, the setting viscosity is measured by a**

Brookfield Model LVT Viscometer. And it's measured by taking the spindle of a Brookfield LVT Viscometer, inserting it in the mixture, mixing for 30 revs per minute for 30 seconds, and then taking the viscosity.

Q. **Is the LVT Viscometer a common piece of laboratory equipment?**

A. **Yes. It is a very common piece of laboratory equipment. In fact, there is one right there. You see, that's the dial, with the reading and the torque. And there is a spindle guard around here. And the spindle sits inside the spindle guard, and what happens, as the spindle spins, the dial reads the drag that the liquid exerts on the spindle. That's how we get a reading of viscosity.**

Q. **In that same section of Column 5 of the '573 patent, how is the shear viscosity described as being measured?**

A. **The shear viscosity is described as being measured in exactly the same way after the composition has been shaken in a Burrell wrist-action shaker at full speed for five minutes.**

Q. **Is the Burrell wrist-action shaker a common piece of laboratory equipment as well?**

A. **Yes, it's very common.**

Q. **What was the first step that you took in preparing to measure the viscosity of Barr's ANDA product?**

A. **Well, the first thing I did was, I prepared a written**

protocol based on the description in the patent, and also based on the Brookfield operation manual, and also based, in part, I know about thixotropic compositions.

Q. Why did you prepare a written protocol?

A. I prepared the written protocol so that I could be absolutely sure that I exactly reproduced the steps that I used when I was doing it. So I followed the protocol exactly to the letter as I was measuring the viscosities.

Q. Calling up Plaintiffs' Trial Exhibit 366, Dr. Lockhead, is this a copy of the written protocol that you just described?

A. Yes, but this is a truncated version I prepared for the, for my first expert report. The full written protocol also included descriptions on how to prepare samples for all of the material that I studied. And some of the samples didn't come in until my second written report.

Q. Turning back to Column 5 of the '573 patent, why did you look to the Brookfield Operating Manual in preparing your written viscosity testing protocol?

A. Because the Brookfield Operating Manual tells one exactly how to operate the Brookfield equipment, and someone who is skilled in the art would, I think, consult the Brookfield manual, or would know the Brookfield manual as I did on how to measure Brookfield viscosity.

Q. Calling up Plaintiffs' Trial Exhibit 363, is this the

Brookfield Operating Manual you were referring to?

A. **Yes, that is the Brookfield Operating Manual.**

Q. **Is this one of the documents you reviewed as part of your work in this case?**

A. **Yes.**

Q. **What information did you find in the Brookfield Operating Manual that would assist in conducting viscosity measurements according to the method described in the patents in suit?**

A. **Well, the Brookfield manual tells you the container size that you should use. It also tells you the working volume of liquid that you should use. And for this case, it told you, told me that I had to use the guard leg, keep the guard leg attached. That's that leg on the viscometer there, the little metal underneath it.**

And these are the container sizes that can be used. What it says is the container has to have an inside diameter of 3.25 inches and a height of 4.75 inches. And the container may be larger, but it may not be smaller to get accurate measurements.

Q. **According to this Page 16 of the Brookfield Operating Manual, what working volumes should be used with the Model LVT Viscometer?**

A. **The working volumes should be 500 milliliters for a 600 -milliliter low form beaker, if the container is a**

600-milliliter low-form beaker.

Q. Does the Brookfield Operating Manual indicate which spindle is appropriate to use?

A. Yes. There are tables in the Brookfield manual that, if you know the target viscosity, and you know the speed at which you have to rotate, you can choose the spindle that would operate in that range. And so you choose your spindle accordingly.

Q. Turning back to Column 5 of the '573 patent, Dr. Lockhead, I believe you said earlier that the patent's description of the compositions as becoming thixotropic informed your understanding of the viscosity method that is disclosed here. Is that right?

A. Yes.

Q. How so?

A. Well, what it does is it describes a setting viscosity and a shear viscosity. Thixotropic liquids recover and thicken up when they are undisturbed. And they are thin when they are shaken or disturbed or shear is applied to them. And in this case, the setting viscosity is specified as 400 to 800 centipoises when the liquid is undisturbed. And the shear viscosity after it's been shaken and in a Burrell reaction shaker at full speed for five minutes is defined to be between 50 and 200 centipoises.

The amount of shaking is very important, because

you shouldn't -- you should follow with a thixotropic liquid, it's very sensitive to shear. So any additional shear or any other actions that would put shear into the system would distort results.

Q. Would the patent's description of the compositions as being thixotropic indicate anything else about the Burrell shaking step?

A. Yes. It would also indicate that you had to use the same container. Basically, what you need to do is you need to use the same container for the shaking and for the measuring because you don't want to introduce any extra shear by transferring liquids from one container to another.

Q. Dr. Lochhead, in your opinion, do the patents in suit set forth a complete protocol for measuring the setting viscosity and the shear viscosity of the compositions that are described there?

A. Yes.

Q. In your opinion, did your viscosity testing protocol conform with the viscosity measurement method described in the patents in suit?

A. Yes.

Q. Did you record your viscosity testing results in a laboratory notebook?

A. Yes, I recorded them in a bound laboratory notebook.

MR. NOE: Calling up Plaintiffs' Trial

Exhibit 484.

BY MR. NOE:

Q. **Dr. Lochhead, is this a copy of the laboratory notebook you just described?**

A. **This is the front page of the laboratory notebook that I described. Yes.**

MR. NOE: We can take that down for now.

BY MR. NOE:

Q. **How did you prepare examples of Barr's ANDA product for testing?**

A. **Well, the samples come in small bottles, and I had to get a working volume of 500 milliliters or more, and so what I did was I transferred the content to the sufficient number of small bottles to get the working volume and the Brookfield viscometer into the container that was sealable so we could put a lid on the container so I could do the shaking. And that's how I prepared the samples.**

And then I allowed the samples to sit for 48 hours before measuring the setting viscosity. That 48 hours might be a little long but I wanted to get a good measure of setting viscosity, and I thought it was prudent to do that because I wanted to do this just once and do it properly.

Q. **And why did you wait for 48 hours before measuring the setting viscosity of the sample?**

A. **I wanted to make sure that I had an undisturbed sample; as I'd said, I was being prudent; and to make sure that the system was truly at rest. When you put a viscometer in, you actually introduce shear, and so that was maybe just a little bit excessive but I thought it was prudent to hold it for 48 hours.**

Q. **Did you calibrate the Brookfield viscometer before conducting viscosity measurements of Barr's ANDA products?**

A. **Yes, one should always calibrate a viscometer, especially in cases like this where you are relying on the results as we are in trial, to make sure that the measurements you are taking are accurate. And so I measured -- I calibrated the viscometer with appropriate viscosity samples.**

Q. **After you calibrated the Brookfield LVT viscometer, how did you measure the setting viscometer of Barr's ANDA product?**

A. **Well, I took the material of Barr's. I took one of the samples of the Barr's ANDA product and each sample corresponded to one lot of Barr's material. So I didn't mix lots. I took one lot and I inserted the appropriate spindle. I mixed it at 30 RPM, 30 seconds, and I read the dial reading. And from there, I calculated the setting viscosity.**

MR. NOE: And I think while you are describing

your viscosity measurements, let's call back up Column 5 of the '573 patent.

BY MR. NOE:

Q. Dr. Lochhead, after you measured the setting viscosity, how did you measure the shear viscosity of Barr's ANDA product?

A. I removed the sample from the Brookfield viscometer and I put it in a Burrell wrist-action shaker, shook at full speed for five minutes and then immediately removed it as quickly as I could, took it to the Brookfield viscometer and measured the Brookfield viscosity after the spindle-head rotated at 30 RPM for 30 seconds. And then I took two more measurements after that 30 second interval, the setting viscosity. I took two more measurements after five-minute intervals.

Q. So a total of three setting viscosity and three shear viscosity measurements for each of Barr's ANDA products?

A. Yes.

Q. And did you measure the setting viscosity and shear viscosity for the other lots of Barr's ANDA product that you received?

A. Yes, I measured it in the same way for all three of Barr's ANDA product.

Q. Did you measure the viscosity of Nasacort AQ in the same manner as you did for Barr's ANDA product?

A. **Yes, I measured the viscosity of Nasacort AQ in exactly the same way, both the setting and the shear viscosities.**

MR. NOE: Calling up Pages 6 and 7 of Plaintiff's Trial Exhibit 484.

BY MR. NOE:

Q. **Dr. Lochhead, do these pages of your lab notebook record the results of viscosity testing of Barr's ANDA product?**

A. **Yes, and what they show is here I've got, before the shake is the setting viscosity; after the shake, the shear viscosity. And what I found was in every case, the setting viscosity was in the range of 400-to-800 centipoise as specified by the claims in the patent as specified by the patent. And the shear viscosity was in the range of 50-to-200 centipoise, as specified by the patent.**

Q. **Calling up Page 10 of Plaintiff's Trial Exhibit 484. Does this page of your lab notebook record the results of your viscosity test of Nasacort AQ?**

A. **Yes. Here are my results from Nasacort AQ, and you see that the viscosity range of Nasacort AQ lies within the range of 400 to 8 00 for the setting viscosity, within the range 50 to 200 for the shear viscosity. And these results verified that my protocol was indeed correct.**

Q. **Do you have an understanding whether Nasacort AQ is a**

commercial embodiment of the patents in suit?

A. Yes, I believe Nasacort AQ is a commercial embodiment. And I believe that Example 1 of the patent is in fact Nasacort AQ.

MR. NOE: And let's call up Column 9 of the '573 patent.

BY MR. NOE:

Q. Is this the example you were just referring to?

A. Yes, and it's my belief that this is Nasacort AQ.

Q. Turning to Plaintiffs' Demonstrative Exhibit 65. Dr. Lochhead, what does this exhibit show?

A. This is a table that is prepared to summarize my results. And what it shows is that Barr's proposed ANDA product falls -- every measurement I took fell within the range of 400-to-800 centipoise for the setting viscosity. That means that it fell within the range that is specified by the patent. And for the shear viscosity, every measurement I took was within the range of 50-to-200 centipoise. That means it fell within the range of the patent.

And also for the setting viscosity of Nasacort, every measurement I took was within the range 400 to 800 for the setting viscosity and 50 to 200 for the shear viscosity. So Nasacort also fell within the range specified by the patent.

Q. **Turning to Plaintiffs' Demonstrative Exhibit 64. What does this exhibit show?**

A. **This is a graphical representation of the same results. And what you see here, this is the range. Here is the viscosity on the bottom axis. And what was showing is the range here for 400 to 800 is the setting viscosity range and you see that Barr's ANDA product falls within that setting viscosity range and so does Nasacort.**

Here, we have the viscosity range for the shear viscosity of 350-to-200 centipoise. And here again, you see that the Barr's ANDA product and also the Nasacort fall within that shear viscosity range.

Q. **Dr. Lochhead, in your opinion, did all of the viscosity testing you conducted conform to the method described in specification of the patents in suit?**

A. **Yes, it did fall within the methods of the patents in suit.**

MR. NOE: Nothing further at this time, Your Honor.

THE COURT: Counsel you may cross-examine.

CROSS-EXAMINATION

BY MR. HURST:

Q. **Good morning, Dr. Lochhead.**

A. **Good morning.**

Q. **How are you today?**

A. **Okay.**
Q. **We met before at your deposition. Correct?**
A. **Yes.**
Q. **Now, counsel offered you as an expert in formulation. Correct?**
A. **Yes, formulation.**
Q. **In fact, you are a cosmetic formulator. That is true. Correct?**
A. **I'm a cosmetic formulator but I also have worked with pharmaceutical compositions.**
Q. **And the patent in this case is about a nasal spray, the formulation of a nasal spray. Correct?**
A. **That's correct.**
Q. **You have never formulated a nasal spray. True?**
A. **I've never formulated a nasal spray.**
Q. **In fact, you have never personally formulated any kind of pharmaceutical formulation. Correct?**
A. **No, I've been part of a team that is formulated pharmaceutical formulations, as shown by my patents. And we took thixotropic formulations and put them in the eye and also bioadhesive polymers that were used as vaginal lubricants. So I've never personally formulated a whole pharmaceutical, myself but I've been part of a team who designed formulations for pharmaceuticals.**
Q. **Just to be clear then, you have, yourself, never**

personally formulated a pharmaceutical product. Correct?
A. I've formulated part of a pharmaceutical product and that is the norm. People often work in teams. By myself, I never completely formulated a pharmaceutical product.
Q. Now, you consider yourself an expert in cosmetic formulation, don't you?
A. I consider myself an expert in formulation. My specialty is cosmetic formulation.
Q. You do not consider yourself to be an expert in pharmaceutical formulation. Correct?
A. I consider myself to be an expert in formulation. That encompasses pharmaceutical formulation.
MR. HURST: May I approach, Your Honor?
THE COURT: Sure.
(Document passed forward.)
BY MR. HURST:
Q. You gave your deposition in this case?
A. Yes.
Q. I'm going to ask you to take a look at Page 13 of your deposition.
A. Page what? I'm sorry.
Q. 13. Dr. Lochhead, if it's easier for you, it's up on the screen. Whichever way you prefer.
A. Okay.
Q. At your deposition, did you give this answer to this

question under oath:

"Question: All right. Do you consider yourself an expert in pharmaceutical formulation?

"Answer: No.

A. I gave that answer.

Q. That's my only question.

A. When you pressed me, I actually, if you go to Page 16, you pressed me, and I said --

Q. That's my only question for now.

A. I said I consider myself an expert in formulations and that would encompass pharmaceutical formulations.

THE COURT: Let me share a thought with you. We are on cross-examination now. So he gets to control the questioning, within reason. I ultimately will make rulings if there are objections that are made by the other side.

But be assured that the lawyers from the other side will question you another round and address these subjects with you.

I understand your point, there was another point in the deposition that gave more context to your answer. Those lawyers for the plaintiff will get a chance to give me that context. Okay?

THE WITNESS: Okay. Thank you.

BY MR. HURST:

Q. Let's provide a little bit of context, Dr. Lockhead.

You have actually never written an article on pharmaceutical formulation. Correct?

A. **I have never written an article on pharmaceutical formulation because my interaction with pharmaceutical formulation tends to be consulting, and you don't normally write articles there. But you got patents.**

Q. **But the short answer is you have never written an article on pharmaceutical formulation?**

A. **I have never written an article on pharmaceutical formulation.**

Q. **You heard me mention in opening the Handbook Of Pharmaceutical Excipients, which I described as the bible for pharmaceutical formulation or something along those lines? You heard me say that. Correct?**

A. **Yes.**

Q. **You have heard of that book. Right?**

A. **Yes.**

Q. **Because I asked you about it at your deposition. Right?**

A. **Yes.**

Q. **You do not have a copy of the Handbook of Pharmaceutical Excipients in your office, do you, sir?**

A. **I don't have a copy in my office.**

Q. **Thank you. You are here today to talk about the infringement issues in this case. Right?**

A. **Yes.**

Q. **You have also offered opinions on obviousness which I presume will be addressed on a different day. For today, it's just infringement. Right?**

A. **Yes.**

Q. **I want to take a look at one of the two claims at issue in this case. It's Defendant's Exhibit 7. Why don't we take, I, there is three viscosity measurements in this claim. Right?**

A. **Yes.**

Q. **It talks about the viscosity of the composition in unsheared form is about 400 to about 800. Correct?**

A. **I can hardly see this on the screen here.**

Q. **Can you see it up here?**

A. **Claim No. 5.**

Yes.

Q. **Is it also blown up on your screen?**

A. **Yes.**

Q. **Now, you have conducted testing to address this particular issue. Correct?**

A. **Yes.**

Q. **Now, pull up II. So that the first one was setting. The second one is shaken or shear viscosity. Right?**

A. **Yes.**

Q. **And that talks about the fact that the composition**

has to have a viscosity that reduces down to 50 to 200 centipoise. Right?

A. **That's right.**

Q. **Centipoise is a measurement of viscosity. Right?**

A. **Yes.**

Q. **Now, there is a third one -- you tested on this one as well. Correct?**

A. **I did.**

Q. **There is a third one here. Why don't we pull up the third one. This one reads, In deposited form on the mucosal surfaces the viscosity of the composition is about 400 to about 800 centipoise.**

Right? Do you see that?

A. **Yes.**

Q. **You did not conduct any testing on this third prong of the claim. Correct?**

A. **That's right, because it's impossible to get good field viscometers into the nose. You can't do it.**

Q. **Well, you could have done relevant testing had you wanted to, couldn't you have?**

MR. NOE: Your Honor, I object as beyond the scope of the expert report. Dr. Lockhead's opening report did not address this third element of the asserted claims.

THE COURT: Is that correct, sir?

MR. HURST: The answer is, he is the only

testing expert in this case. He did no testing on this element. The expert that follows is relying on Dr. Lockhead's testing. So he is the witness to cross-examine on this point.

THE COURT: I will overrule the objection.

BY MR. HURST:

Q. Now, you could have, had you wanted to -- just to confirm what I told Your Honor, you are, in fact, the only expert, that you are aware of, at least, you are the only expert on Aventis's side who conducted any testing of Barr's product. Correct?

A. That's correct.

Q. So as far as you know, nobody conducted any testing on this third element of the asserted claim. Correct?

A. I didn't test the third element, and as far as I know, none of the witnesses did testing for that third element.

Q. What you said to Judge Sleet was, there is no way to do it because you can't put the Brookfield Viscometer up somebody's nose. Right?

A. That's right.

Q. But you could have, had you wanted to, conducted relevant testing. Correct? Let me give you an example. You are hesitating.

Can I give you an example?

A. **Yes.**

Q. **You know, for instance, that when Barr's product is deposited in somebody's nasal cavity, it will be cleared in about 30 minutes or so, according to the patent. Correct?**

MR. NOE: Objection, Your Honor. Again, this is beyond the scope of Dr. Lockhead's expert report. It does not contain any discussion of mucociliary --

THE COURT: He is using this as an exemplar in order to set up a question that I have already ruled is in order. So the objection is overruled.

THE WITNESS: Could you repeat the question?

BY MR. HURST:

Q. **Sure, no problem. You see from the patent -- you have read the patent. Right?**

A. **Yes.**

Q. **You see in the patent when something gets deposited in the nose, it's gone in ten to 30 minutes, I think the patent says. Right?**

A. **I think it says longer than that. For this particular composition, I think it was longer than that.**

Q. **Let's take a look at Defendant's Exhibit 7, at 4, Column 10, do you see where it says such forces, referred to as mucociliary clearance, are recognized as being extremely effective in removing particles from the nose in a rapid manner, for example, within ten to 30 minutes from the time**

the particles enter the nose?

Do you see that?

A. That's generally, from my reading --

THE COURT: Counsel, he has not opined in this regard, as I understand.

MR. HURST: I am using the question exactly as you said.

BY MR. HURST:

Q. Here is my question: You could have, had you wished, tested Barr's product after letting it rest for 30 minutes to see whether even if on the tabletop it would return to setting viscosity within 30 minutes. You could have done that. Right?

A. With a Brookfield Viscometer, which is the instrument that's specified, you are actually putting shear into the mixture as you are measuring it, it's a thixotropic mixture. So on the tabletop, with that amount of volume, you are disrupting the structure as you measure it.

I may have been trying to measure that one.

Q. I am asking whether you could have done it. You had Barr samples in your laboratory. Right?

A. Yes.

Q. Why don't we look at what you did.

Let's pull up Defendant's Exhibit 362.

Why don't we just take an Example No. 3. Pull

up No. 3 and blow it up.

Agis is Barr's product, as you understand it. Right?

A. Yes.

Q. You measured setting viscosity and shear viscosity. Right?

A. Yes.

Q. Now, what you did when you prepared the samples, before you measured for setting, you actually had to cut open the bottles and pour the material out. Right?

A. Yes.

Q. And that created shear?

A. Of course.

Q. And then, because you wanted to get at setting viscosity, you had to let it rest before you measured it after you created the shear. Right?

A. Yes.

Q. And you didn't let it rest merely 30 minutes, did you?

A. No, because I didn't know how much shear I put in and shaken and putting those little bottles out then. That may have been a very large amount of shear where I disrupted the whole structure. The structure is just a bunch of particles. And I wanted to make sure that it was, indeed, a true setting viscosity. And I may have really disrupted

that structure by pouring the bottles out.
Q. And the worry that you had is, after you introduced shear, it might take an awful long time for the product to get back to setting viscosity. Right?
A. Well, yes, thixotropic materials where the amount of shear you put in, the structure is broken to different extents by different shear. My concern was --
Q. Your Honor --
A. -- was that I put a lot of shear in there.
THE COURT: Go ahead.
BY MR. HURST:
Q. My only question, now Dr. Lockhead, is the -- you waited 48 hours, didn't you?
A. I did.
Q. And the reason you as an expert in viscosity and thixotropic materials waited 48 hours before you measured setting is because it can, in fact, take a really long time after you shear a material for it to return to setting viscosity. True?
A. If I have completely broken the structure, yes.
Q. So after you waited 48 hours before you measured setting viscosity, you then measured shear viscosity. Right?
A. Yes.
Q. You first did setting and you did three measurements,

it went from 606, 600, and 588. Right?
A. Yes. That, in fact, shows the effect of shear on the system as I was --
Q. Dr. Lockhead, we have time limits in this case. If your counsel wants to ask you more, he is perfectly free to do so.
So after you did the setting viscosity, then you measured shear. Right?
A. Yes.
Q. Now, after you sheared it up, and introduced the shear and mixed it, it took a little while before you actually got around to measuring it, right, like anywhere from 30 seconds to a minute? Correct?
A. About 30 seconds to a minute, yes.
Q. One thing we know is that in 30 seconds or a minute, the material, Barr's material, did not return to its setting viscosity. Right?
A. As measured by a Brookfield Viscometer.
Q. That's what the patent talks about, sir. Right?
A. The Brookfield -- measured by a Brookfield Viscometer.
Q. Do you see where it says 98 right here?
A. Yes.
Q. That's one-sixth -- setting viscosity is 600 percent more. Right? Six times as high. True?

A. **Yes, the patent says measure the shear viscosity and the setting viscosity.**

Q. **Okay. Now, then you waited another 30 seconds. Right?**

A. **Yes.**

Q. **And you got a viscosity of 102. Right?**

A. **Yes.**

Q. **So it still didn't return to its setting viscosity. True?**

A. **That's true in structure build-up, yes.**

Q. **And then it actually goes down to 96.8. That's just variability, I take it. Right?**

A. **It could be variability. It could be shear induced by the spindle.**

Q. **In either event, this is anywhere from a minute and a half to two minutes. Correct?**

A. **Yes.**

Q. **On the third measurement. So here you take your material, a minute and a half to two minutes later, we are still nowhere near setting viscosity. Right?**

A. **Yeah, and I am measuring a very large volume, with the Brookfield.**

Q. **So, now, one of the things you could have done in this case, and this is what I am asking you about, you could have said, well, how long does the material stay in the**

nasal cavity, 30 minutes, an hour, whatever it is, and you could have measured Barr's product to see if even on the tabletop it returns to setting viscosity in the same amount of time you would expect it to be in the nasal cavity? You could have done that. Right?

A. **I could have done that with the Brookfield Viscometer, but I didn't.**

Q. **You didn't do that. There was nothing physically stopping you from taking that measurement to try to see how quickly Barr's product returns to setting viscosity. Right?**

A. **I would have had to have left the material at rest without disturbing with the Brookfield for a certain length of time.**

Q. **And you are capable of doing that. Right?**

A. **Yes.**

Q. **Because you did it for 48 hours before you measured setting so you could have let it rest 30 minutes. Right?**

A. **On the Brookfield Viscometer, I could have let it rest for 30 minutes.**

Q. **That's what I am asking about.**

Then you still had the samples, they were available, you still had the Brookfield Viscometer, there was no reason in the world that you couldn't have just simply measured Barr's product to see if it recovered its setting within --

THE COURT: Counsel, the question is argumentative.

BY MR. HURST:

Q. **Let me ask you this: Who made the decision not to do the testing that determined whether Barr's product returned to setting in the amount of time Barr's product would be expected to be in the nasal cavity?**

MR. NOE: Objection, Your Honor. Lack of foundation.

THE COURT: Sustained.

BY MR. HURST:

Q. **Now, let's take a look at Defendant's Exhibit 23 at 97. Now, you have seen this testing as represented in this laboratory notebook page before. Correct?**

A. **Yes.**

Q. **Can we highlight at the very top the subject matter line. You see, this is about the viscosity of Nasacort versus Beconase. Do you see that?**

A. **Yes.**

Q. **And you see that the purpose is test viscosity of our product versus Beconase and Vancenase, to see if they return to their unshaken state at equal times.**

Do you see that?

A. **Yes.**

Q. **Now, go to the first line, Unshaken. See where it**

says Unshaken right here?
A. I think it says that, yes.
Q. You understand these two to be Nasacort. Right?
A. Yes.
Q. You see this setting viscosity they got, 3460, 3060, 3640, 3240?
A. Yes. And these are very high viscosities. So I don't know if they were measured the same way as I measured them.
Q. Well, you know these were measured at 6 RPMs and the patent refers to 30 RPMs. Right?
A. Yes. And 6 RPM would induce a lot less shear than 30 RPM.
Q. There is a conversion you can do, when you do six RPMs versus 30 RPMs, you would just divide those numbers by five to give yourself an estimate of what it would look like at 30 RPMs. Right?
A. For Newtonian liquids, yes. But for non-Newtonian liquids, it is not necessarily a linear relationship. So for thixotropic liquids, you can determine by something different on something we call thixotropic glue, which gives you different viscosities.
Q. In any event, here is the unshaken viscosity or the setting viscosity they got. Now, let's go to six hours later. Leave them both up. See the test at six hours. And

the numbers they get are still one-third of the setting viscosity. Right?

A. **Yes. But they are much higher than the viscosities as applied in the patent. So what it shows is that the measurement depends on -- the viscosity you get depends on how the measurement goes. And here we are running at six RPM, which is a much less disturbing measurement, so you don't disturb the structures.**

Q. **Just relatively, that is all I am talking about. They were looking at recovery rates, isn't it true that even after six hours, Nasacort was still only one-third of its setting viscosity, according to these experiments? Is that true?**

A. **At 6 RPM in a Brookfield Viscometer, those results say that, yes.**

Q. **Now, let me talk real briefly about your testing protocol. I am going to move on to a slightly different topic than your testing protocol.**

Let's talk about the nasal cavity. Can we go back to III again of Claim 5 of Defendant's Exhibit 7.

Now, we were talking about, earlier we were talking about III. Right?

A. **Yes.**

Q. **In deposited form on the mucosal surfaces. Right?**

Now, that is inside the nasal cavity, obviously.

Right?

A. **That's what it says, inside the nasal cavity, yes.**

Q. **Now, however long it takes for Barr's product to return to its setting viscosity on a tabletop, you would expect it to take even longer inside the nasal cavity. Correct?**

A. **I don't know. I am not an expert in the nasal cavity.**

Q. **You know at least that the nasal cavity is a different environment than sitting on a tabletop. Right?**

A. **It probably does.**

Q. **You know, for instance, that the nasal cavity is going to have a higher temperature than room temperature. Correct?**

A. **Yes. I was in court yesterday when you said part of it, the reason, the function of the nasal cavity is to warm the air on the way in.**

Q. **Now, let me ask you directly, it's true, is it not, that higher temperatures cause material generally to become less viscous, not more viscous, as required by the patent?**

A. **Not necessarily. Some polymer solutions get less viscous, some get more viscous, as you raise the temperature. And here you have got polymer plus particle, and it could go either way.**

Q. **But you didn't do any testing on Barr's product, did**

you, to see how it would react at 98.6, did you?
A. No, because I am not an expert in the nasal cavity.
Q. That's fine. There was nothing physically stopping you, was there, from testing Barr's viscosity at temperatures that would match the temperatures of the mucosal surfaces in the nose as required by the patent. You could have conducted testing at higher temperatures. True?
A. I could have conducted bench temperatures at 500 milliliters on a Brookfield Viscometer at 37 degrees Celsius, yes.
Q. But you did not do that. Correct?
A. I didn't do that, because I am not an expert in the nasal cavity.
Q. But you are an expert -- all right.
Let me ask you this: With respect to the composition, Barr's composition, there is a reason to believe that higher temperatures would make it less viscous, not more viscous. You agree with that. Right?
A. I am sorry, could you repeat the question?
Q. Sure. We are talking about Barr's nasal spray, and I asked you how temperature would impact it. You agree that there is a good reason to believe that higher temperatures would cause Barr's product to become less viscous, not more viscous?
A. No, I don't know that, because a particular

dispersion, it could go either way, and I haven't measured it.

Q. Let's go to your deposition, Page 102. Beginning at Line 5, to Line 14. At your deposition Dr. Lockhead, did you give this answer to this question:

"Question: Just your general expertise in thixotropic components doesn't allow you to surmise that an increase in temperature would impact viscosity of these claimed fluids one way or another?

"Answer: CMC" -- that's one of the ingredients in Barr's product. Right?

A. That's correct.

Q. "CMC would lose viscosity, and that's a component of this mixture so you may think you would see a loss in viscosity."

Did you give that answer to that question, sir?

A. Yes. And that's what I have been saying, that's only one component.

Q. Now, another difference between tabletop testing and the nose is nasal secretions. Right?

A. I guess so.

Q. Nasal fluids can also impact the viscosity of a formulation. Isn't that true?

A. I don't know. I haven't measured it. But I surmise it's true.

Q. **Cilia in the nose, you saw the video yesterday, the cilia?**

A. **Yes.**

Q. **You understand that cilia, they beat and they actually shear mucus. Correct?**

A. **According to Dr. Berridge's --**

MR. NOE: Your Honor, I must object again. This is far beyond the scope of his opening expert report. None of his material in that report addresses nasal anatomy, ciliary action, dilution by mucus secretion. We are well beyond the scope here.

THE COURT: Your response?

MR. HURST: Your Honor, they don't have an expert to address the issue of whether Barr's product returns to setting viscosity in the nose. Dr. Lockhead, I think, is probably the closest we have or perhaps the next witness, Dr. Prud'homme, I think this is fair cross-examination.

Dr. Prud'homme and Dr. Lockhead are the only two witnesses, I believe, that are actually testing -- testifying about these substantive issues relating to infringement. So I think this is fair cross.

THE COURT: Do you agree with your opponent's statement as to the status of witnesses who are going to be able to talk about this particular subject?

MR. NOE: Yes, Your Honor. Dr. Lockhead and Dr. Prud'homme are two witnesses that are going to discuss viscosity.

THE COURT: Well, why would you want the fact-finder to hear from these witnesses with regard to their expertise in measuring what is being discussed and what he is now talking about, these other things, like cilia, that may impact upon the issue of viscosity and consequently whether there is infringement or not? Please.

MR. NOE: Your Honor, in the case of Dr. Lockhead, our position is that it would be speculative in light of the contents of his opening report.

THE COURT: Is it beyond his area of expertise? Testing is I think why you called him, the tests that he performed?

MR. NOE: The testing that he performed is certainly within his expertise. The effect of the nasal environment on solutions deposited there is beyond his expertise.

THE COURT: Now he is being asked as an expert to discuss how outside elements might impact, or have impacted testing that he did or didn't do.

That's not fair game, in your view?

MR. NOE: It is, again, Your Honor, it is speculative in our view.

THE COURT: I am not sure that it is speculative. I am going to permit you to continue.

I will overrule the objection.

BY MR. HURST:

Q. **Thank you, Your Honor.**

Cilia in the nose, you understand that cilia have the ability to shear and thin materials in the nose. Correct?

A. **I listened to the expert testimony yesterday. And from that, I understand that there is a viscous layer that the cilia beat in and the mucus actually lies above that layer and shears that layer. And the mucus is a polymer system, a polymer solution, a polysaccharide, very much like the big polymers.**

Q. **You saw in the video yesterday there was mucus in some places and no mucus in other places. So you would expect the material to interact with the cilia?**

A. **I don't know that it does interact or doesn't interact with the cilia.**

Q. **At the very least, though, that kind of movement, a thousand beats a minute, as an expert in viscosity, will you at least agree with me that that thousand beats per minute actually introduces shear, which lowers viscosity? Will you agree with that?**

A. **It would introduce some shear into the aqueous layer.**

In the aqueous layer, I don't know if it would decrease the viscosity.

Q. **You did no testing one way or another to try to determine how that level of shear would impact the viscosity of nasal formations in the nose. Correct?**

A. **No, no.**

Q. **Now, I just want to put a fine point on this so it is totally clear.**

Can we go to Claim 5 of the '573 patent again.

On this third element of the claims, you have no opinion one way or another about whether Barr's product meets III. Correct?

A. **No, I have no opinion.**

Q. **Thank you. I want to talk now briefly about the frontal sinus issue. You heard yesterday that Dr. Berridge was relying on your testing for some of his testimony. Correct?**

A. **I think so, yes.**

Q. **I want to talk to you about that. Why don't we put up -- let me just make sure this is all in context. Dr. Berridge, like you, did not do any testing on Barr's product. Is that true?**

A. **I did do testing on Barr's products.**

Q. **My mistake. I was actually referring, I was thinking about III, I stand corrected. You tested Barr's product for**

I and II. Right?

A. **Yes.**

Q. **My apologies.**

Dr. Berridge did no testing, as you understand it, on Barr's product?

A. **That's correct.**

Q. **And he only tested Nasacort. Correct?**

A. **No. I think he tested Nasacort and Flonase.**

Q. **And Flonase, okay.**

Now, his testimony yesterday was that my testing on Nasacort with respect to this frontal sinus issue is good enough to prove that Barr's product gets to the frontal sinus because the products were, in his words, identical. Do you remember that?

A. **Yes.**

Q. **Now, let's take a look at Plaintiffs' Demonstrative Exhibit 65. Point 1.**

Counsel showed you this in direct. Right?

A. **Yes.**

Q. **Now, when the product is entering the nose, the relevant viscosity measurement we are talking about is not really the setting, but it's the shear viscosity. Right?**

A. **Yes. The shear viscosity of that spray.**

Q. **So Dr. -- well, you tested Nasacort's shear viscosity and you got numbers 61 to 68. Right?**

A. **Yes.**
Q. **You tested one lot. Right?**
A. **Yes.**
Q. **Do you have any idea whether the material that Dr. Berridge tested in 1996, in 1998, do you have any idea whether it was identical in shear viscosity to the lot that you measured here?**
A. **It may not be identical. But you got lot-to-lot variability.**
Q. **Sure. Now, with respect to Barr's product, you actually have a much higher shear viscosity than 61 to 68. Right?**
A. **Yes. And that again reflects lot-to-lot variability all within the range.**
Q. **It's actually at least 60 percent higher?**
A. **Than the one lot that I measured, yes. But it still falls within the range. That is why you have ranges, because it is very difficult to get things identical, that you have natural changes in manufacturing, you have changes in materials. So you put ranges in there. And it falls, they all fall within the range.**
Q. **Sure. That's actually my point. Even manufacturing from one location to another location could impact the viscosity measurements that you ultimately get in a product. Right?**

A. **Yes. You get lot-to-lot variability.**

Q. **You understand that Barr manufactures its product at a different location than Aventis manufactures its product. Right?**

A. **I think so.**

Q. **When you tested, you found that Barr's product, at least the three lots that you tested, had much higher shear viscosity than Nasacort. Right?**

A. **They had higher shear viscosity. But it was still within the limits specified.**

Q. **The limits specified where, sir?**

A. **In the patent.**

Q. **Actually, now I am just focusing on Dr. Berridge's testing. He didn't test, as far as you know, as far as you know, Dr. Berridge never conducted any tests about whether a product with viscosity at around 100 could reach the frontal sinus?**

A. **I don't think he did any viscosity testing.**

Q. **But he tested a product that at least according to your testing is about 60 or so. Right? That's what he tested?**

A. **That one lot was 60. I don't know if he -- what lot he tested.**

Q. **He could have tested lots that were even lower than 60 as far as you know. Right?**

A. **They could be as low as 50, but no more.**

Q. **So you have no idea, do you, whether a product with the viscosity that you have shown for Barr at around 100 has the capability of getting into the frontal sinus?**

A. **I have no idea of anything getting into the frontal sinus. It is not my expertise. But I don't know whether the lot-to-lot variability would affect that.**

Q. **And Dr. Berridge, you didn't hear him testify, either, about whether lot-to-lot variability and shear viscosity could impact whether a product gets into the frontal sinus. Right? You didn't hear him talking about that?**

A. **No.**

Q. **What he did testify about is -- do you remember his 2002 studies?**

A. **Yes.**

Q. **Where he came up, he tested those, and for 12, I think it's 12 people, he got a zero, zero, zero 12 times, nothing in the frontal sinus. Do you remember that?**

A. **Yes.**

Q. **And he had an explanation. Right? Do you remember his explanation?**

A. **Yes, it was the middle of the winter and he transferred it in his trunk.**

Q. **Yeah, because temperature can impact viscosity.**

Right?

A. **It can impact viscosity and stability. You can get freeze-frost stability, which essentially causes a product to separate.**

Q. **I am on viscosity right now. Temperature can impact viscosity. Right?**

A. **It can impact viscosity.**

Q. **So it's possible, isn't it, it's possible, that what happened is, he takes a product with 61 to 68 shear viscosity, puts it in his car, it gets kind of cold, and it goes up to a hundred. And that explains why he got no frontal sinus deposit. That's possible, isn't it?**

A. **That's one thing that is possible. Another possibility, as I said -- I lived in Cleveland. I know how cold it gets in Cleveland. In the winter, you can get formulations to freeze. As soon as you freeze, you can actually get separation. He could end up with most of it at the range of the spray.**

Q. **But we have no data about whether the formulations that he tested had viscosities in this range. Correct?**

A. **No, we don't have any data.**

Q. **But we do know that when it got cold, suddenly, and you are surmising that increased the viscosity. Right?**

A. **No, no.**

Q. **He was?**

A. **I think you are surmising that.**
Q. **And that's what prevented the frontal sinus deposit? That's what he said prevented the frontal sinus deposit, the higher viscosity. Right?**
A. **I don't remember him saying that. He said the conditions were different and the temperature was different.**
THE COURT: Why don't you leave it to me to remember what Dr. Berridge said.
MR. HURST: Fair enough.
BY MR. HURST:
Q. **I am going to turn to a different topic. Let's go to protocol real quickly.**
Can we put that up on the screen. 366.
This protocol is three pages long. Right? Two and a half, I think, actually?
A. **I think so. I will accept that.**
Q. **Single-spaced. Right?**
A. **Yes.**
Q. **And you tested both the prior art products and Barr's product using this protocol. Right?**
A. **No, a longer protocol I used for, to describe all of the products. I selected this particle protocol for my opening report.**
Q. **You have a different protocol for testing the prior art products?**

A. **It's the same protocol.**

Q. **It's longer?**

A. **They are parts of the same protocol because in my first report I was only dealing with Barr's products and Nasacort. In my second one I was also dealing with Flonase and Beconase. So I included them in the second part.**

I was following the same protocol.

Q. **I thought this was going to be my only chance to talk to you about your protocol. If you are actually going to talk about a different protocol for the prior art products, I will save my cross for that.**

A. **It wasn't a different protocol.**

Q. **But it's a little longer, that's all. Right?**

A. **It was prepared for the report.**

MR. HURST: Your Honor, I have no further questions.

THE COURT: Any redirect?

MR. NOE: Your Honor, just a few questions.

REDIRECT EXAMINATION

BY MR. NOE:

Q. **Dr. Lockhead, do you recall that Mr. Hurst discussed Page 13 of your transcript from your deposition, where he asked you the question of whether you considered yourself to be an expert in pharmaceutical formulation?**

A. **Yes, I recall that.**

Q. **If we could call up Page 16 from his deposition. Do you recall that Mr. Hurst asked you that same question again, I believe you were talking about that earlier, at Line 19, beginning at Line 18:**

"Question: But you don't consider yourself to be an expert, do you, in pharmaceutical formulations much like thixotropic formulations?"

And your answer there was, "I consider myself an expert in formulations and that would encompass pharmaceutical formulations."

Is that correct?

A. **Yes.**

Q. **And at Page 102 of your deposition transcript, which Mr. Hurst also discussed with you, on the issue of the possible effect of temperature on viscosity, Mr. Hurst showed you the beginning of the deposition transcript. I just wanted to discuss with you whether you recall the discussion that continued directly thereafter, and at Line 16 Mr. Hurst asked:**

"Question: As the temperature rises?" And your answer there was, "Yes, but it's a complex fluid so you can get a difference in structuring which may give you an increase in viscosity. In fact, some of these fluids go up and down in viscosity with temperature and pressure."

Do you recall that?

A. **Yes, I recall that, and I did say that. That's what I tried to say today as well. That's my understanding.**

MR. NOE: Thank you, Your Honor. Nothing further.

THE COURT: All right. Thank you, Doctor.

(Witness excused.)

MR. BERGHOFF: We are ready to call our next witness, Dr. Robert Prud'homme.

... ROBERT KRAFT PRUD'HOMME, having duly sworn as a witness, was examined and testified as follows ...

MR. BERGHOFF: May I approach the witness, Your Honor?

THE COURT: You may.

Good morning, Doctor.

DIRECT EXAMINATION

BY MR. BERGHOFF:

Q. **Dr. Prud'homme, would you repeat your name for us?**

A. **My name is Robert Kraft Prud'homme.**

Q. **And briefly summarize your education for us, if you would?**

A. **I received my Bachelor of Science in chemical engineering from Stanford University. After a time in the Army, I was in the graduate program in pharmacological science and public policy at Harvard University. That was following up some of the environmental science problems I**

was working on in the military. Then I decided to return to more technical background and obtained my Ph.D. at the University of Wisconsin.

Q. And when did you obtain your Ph.D.?

A. 1978.

Q. And what subject was the Ph.D. in?

A. It was in rheology, the flow of complex fluids.

Q. We have heard the term rheology a few times. What is rheology, maybe in very simple terms?

A. Rheology is the study of the flow of materials. So when you put a force on it, how the material moves.

Q. Does that include within it the study of viscosity?

A. Yes. Viscosity would be one of those ways one would characterize its motion.

Q. Thank you. Now, could you describe for us your work or professional experience after obtaining your Ph.D.?

A. So I have been a faculty member at Princeton University since that time. I am the director of the program of engineering biology at Princeton University. I lead the National Science Foundation Center on nanoparticle formulation, generally directed to drug compositions.

I have had sabbatical leaves at Bell Labs and the University of Sidney in Australia.

Q. So you have been at Princeton as a professor from 1978 to the current time?

A. **Yes.**

THE COURT: That's what he said, counsel. You don't need to rehash it. I am listening. I really am.

MR. BERGHOFF: Point taken, Your Honor.

THE COURT: It may seem at times that I am looking over there. But I really am listening.

BY MR. BERGHOFF:

Q. **Do you teach classes as part of being a professor at Princeton?**

A. **Yes, I do.**

Q. **Do you teach any classes that relate to pharmaceuticals or pharmaceutical formulations?**

A. **Yes. Actually, I just finished and gave my final exam last week on bio-separations to undergraduate chemical engineers. That course covers the technology of science and engineering issues in pharmaceutical product manufacturing.**

Q. **Does that include formulations within that?**

A. **That would be a component of that, yes.**

Q. **And what level is that? That's undergraduate? Graduate?**

A. **That's undergraduate.**

Q. **You mentioned that you were a director at a nanoscience institute. Could you expand on that a bit and tell us what that is?**

A. **This is coming out of our research program, we were**

successful in winning a National Science Foundation Center for this technology of making small nanometer-size fractions, diameter of human hair particles, which have particular properties that make them advantageous as carriers for drugs.

And at that center, I lead their faculty members at Princeton doing simulations and computer modeling of these processes, professors at the University of Ohio State, doing some flow properties involved in this formation, and some professors at the University of Minnesota doing some of the polymers that are used in these processes.

Q. And is drug formulations, pharmaceutical formations involved in the work of that Nano Institute?

A. The Nano Institute is the scientific base. Many of the collaborations that come from that, that is, the industrial sponsors, industrial people who come and sort of follow our work are related to drug formulation issues. So we have sponsorship in a company that is using our technology to look at imaging agents, drug delivery and imaging agents, how you control the release -- another company -- how you control the release of drugs out of nanoparticles. Merck has sent two of their researchers to study this process.

Q. Do you hold any honorary positions in your field of expertise?

A. **Well, if, by honorary position, I'm the President of the U.S. Society of Rheology. I have the Excipient National Science Foundation Young Investigator Award, earlier in my career. And I've been named to several distinguished visiting lectureships.**

Q. **Do you serve on any executive committees of any organizations, in the scientific areas?**

A. **I served on the American Institute of Chemical Engineers, Material Science Division as well as earlier on the Executive Committee of the U.S. Society of Rheology.**

Q. **Do you do any consulting with industry?**

A. **I do a considerable amount of consulting with industry so I have consulted with major U.S. chemical companies: Dow, DuPont, Hercules here in Wilmington. In the energy area, Exxon, Mobil and also considerable consulting in the pharmaceutical industry. I've consulted with Merck, Bristol-Myers Squibb, Abbott, GlaxoSmithKline, Block Drug Company, Johnson & Johnson.**

THE COURT: When did you consult with Hercules?

THE WITNESS: I was there about --

THE COURT: If you remember what year? Just roughly.

THE WITNESS: My last visit was six months ago, and I began about 20 years ago.

THE COURT: I might have been there. Okay. I

just wanted you to know. We've never worked together.

THE WITNESS: No.

BY MR. BERGHOFF:

Q. The work you describe, the consulting work you describe for pharmaceutical companies, did it involve pharmaceutical formulations?

A. Yes it did. In my expertise in polymers, rheology, complex fluids, it would be addressing issues in that sector of a problem in drug formulation or drug production.

Q. And have you ever taught any courses at any of companies with which you have consulted in the pharmaceutical area?

A. Yes, I have been asked to teach short courses in my area of expertise at Abbott Labs, for example, and at FMC for their formulations group as they sell into the pharmaceutical industry.

Q. Now, you mentioned FMC. You consulted with them, I take it?

A. Yes.

Q. What was the subject matter of that consultation?

A. Their chief scientific technologist was a person named Wyman Morgan. He established a high level scientific advisory committee; and he would call us in to address various scientific and engineering challenges they were having and to give them corporate strategic direction.

Q. **Did it relate to any particular products of FMC?**

A. **The entire spectrum of products. The particular issue relating to this is we were asked in one occasion to address issues of the processing and structure property relationships for Avicel, that is, how can the process change the material that they make, and another in how uses of Avicel, specifically in pharmaceuticals, how they would increase their market share in that area.**

Q. **And Avicel is one of the ingredients in both Nasacort and the Barr product?**

A. **Yes, it is.**

Q. **You have publications from your research, I assume, Dr. Prud'homme?**

A. **Yes, I do. I have over 200 publications.**

MR. BERGHOFF: And, Your Honor, Dr. Prud'homme's CV is already in evidence as PTX-377. And I would offer Dr. Prud'homme at this point as an expert in the properties of viscous compositions and formulations.

THE COURT: Any objection?

MR. HURST: No objection.

THE COURT: The doctor is accepted as an expert in that field.

BY MR. BERGHOFF:

Q. **And I'll ask because I've save potentially my opposing counsel the time. Have you ever personally, just**

yourself, prepared a pharmaceutical formulation?

A. My answer to that is somewhat indirect. That is, I don't believe that one person does a pharmaceutical formulation the same way that not one lawyer is doing this case between Barr and Aventis. There is a team. Everyone on that team has a function, a purpose, an expertise.

I've been involved in providing expertise in the areas of polymers and delivery mechanisms involving polymers in those companies I've consulted for as well as in our research, as I mentioned, with nanoparticles. Our technology licensed our technology both for forming the nanoparticles to deliver anti-cancer agents and the release of those anti-cancer agents.

So have I been involved in pharmaceutical formulation? I believe the answer to that is yes, but I don't believe myself nor any one individual does the entire job.

Q. Thank you. Just some technical background questions. First, you told us what rheology is just a moment ago. What is viscosity in very simple terms?

A. Viscosity is a measure of the thinness or thickness of a fluid.

Q. And can you give us some examples maybe from our common experience of very thick or very thin fluids so that we can get a handle on this?

A. **In these units of centipoise that the trial is talking about, if you add water, that would be one centipoise, so tipping water back and forth. If you have olive oil, that is about 100 centipoise, tipping that back and forth. If you have a heavy grade motor oil, that is about 1,000 centipoise, tipping back and forth. So that is the range of numbers we're discussing here and that is sort of what they look like if you tip them back and forth.**

Q. **If you could give us an example of a highly viscous material that would be well above the 1,000 centipoise range?**

A. **Things such as asphalt or chalking adhesives would be much higher than that.**

Q. **What does it mean to be thixotropic? Again, just in simple terms.**

A. **It means that the material will become thin when it's shaken or deformed. When stress is put on it, you get thinner, less viscous. When that stress disturbance is removed, it becomes more viscous, and there is some time that it takes to do that transition from more to less viscous.**

Q. **Could you give us an example again from our everyday experience of viscous composition?**

A. **An example of one that is viscous and thixotropic would be ketchup. So in a bottle, if you turn the bottle**

upside down, the ketchup may remain in the bottle. It's in this high viscosity state. When one shakes the bottle, now one can pour it out because in that process of shaking, one has decreased the viscosity that will flow out. The structure will rebuild, and that ketchup will stay on top of the french fries or whatever you put it on.

Q. You're familiar with Nasacort AQ from your work on this case, Dr. Prud'homme?

A. Yes, I am.

Q. And is or is not Nasacort AQ thixotropic?

A. It is thixotropic.

Q. And what makes it thixotropic?

A. It's formulated with a polymer-dispersing agent called Avicel 611.

Q. And is that dispersing agent, as you call it, is that sometimes called a suspending agent?

A. Yes, that would be another term for those.

Q. And Avicel's 611, is that made by FMC? Did you talk about that before?

A. Yes, it is.

Q. What is Avosil 611?

A. Avosil 611 is a single material that is made by intensively by milling or mixing under high intensity microcrystalline cellulose and a polymer called CMC.

Q. And did you prepare a diagram that would help us

understand the structure and characteristics of Avicel?
A. Yes, I did.
MR. BERGHOFF: Let's put up Plaintiffs' Demonstrative Exhibit 51.
BY MR. BERGHOFF:
Q. And could you explain to us what is shown here, perhaps panel by panel, starting from the left?
A. On this panel, the stars are to represent what is called microcrystalline cellulose. And microcrystalline cellulose is cellulose coming from wood. Wood would be a chunk of material that would have no value. So one disrupts that wood structure to get down to the very fine microfibrils, which are those star structures. So they're like tumbleweeds of the cellulose structure, wood structure.
If one just had those tumbleweeds, that material would aggregate rapidly, fall to the bottom and have no efficiency or efficacy as a suspending agent or a viscosifying agent.
In that processing step, it is, as I said, co-processed with the orange worms in that picture which represent the carboxymethylcellulose. Again, the cellulose molecules. Now it has charge groups on it.
The processing welds together those negatively-charged carboxymethylcellulose with the tumbleweed microcrystalline cellulose structure. What

that does is one tunes the sizes of these tumbleweeds and the carboxymethylcellulose is tuning the stickiness of the tumbleweeds. So therefore even if one gives the same carboxymethylcellulose microcrystalline cellulose composition, that doesn't mean the Avicels are similar. It depends on the process and how collapsed or open these tumbleweeds are and how tightly bound the carboxymethyl-cellulose is to the tumbleweed. So one no longer has two different polymers. Avicel is one subject, one species at this point.

Q. Dr. Prud'homme, let's just stay on the left panel, if we could. This is labeled unsheared structure. What does that mean?

A. So this is saying at rest. The microcrystalline cellulose, the Avosil material is, these tumbleweed structures are bonding together, linking together to form a three-dimensional network, and that three-dimensional network is a gel-like material. It looks like ketchup at rest.

Under shear, those tumbleweeds are broken apart rapidly. And when they're broken apart -- and the middle structure shows they're free flowing and the viscosity is reduced, much lower. When one removes the shear, those tumbleweed structures quickly reattach to each other and that structure, that gel-like structure rebuilds quickly.

Q. **So the center panel shows us the structure after some shear has been put on the material?**

A. **Yes.**

Q. **And the panel on the right shows what happens as the structure recovers?**

A. **Yes.**

Q. **Is the structure, the recovered structure on the right always exactly the same as the original structure on the left?**

A. **No, it's a random process. So the viscosity properties will be the same if one measures it appropriately. However, the details of how they go back together, it's a random process. You have slightly different microstructures.**

Q. **Are you familiar with the properties, the viscosity properties, the thixotropic properties of Avicel CL 611, the particular suspending agent used in Nasacort and in Barr's accused product?**

A. **Yes, I am.**

Q. **And how quickly does an Avicel CL 611 suspension recover its structure after shear is removed?**

MR. HURST: Objection, Your Honor.

THE COURT: Basis.

MR. HURST: This is outside the scope of his expert report. I can stand to be corrected but this is

something that is not at all familiar to me.

THE COURT: Is he correct, counsel? I would be actually surprised if it were outside, but go ahead.

MR. BERGHOFF: Your Honor, in Paragraphs 37 and 38, he is talking about the measurements in two reports: the Hydan report and the FMC report. In specifics, we're just doing it in general now, that deals with the recovery properties of the material that include Avicel CL 611.

MR. HURST: This is outside the scope of his report. The question now is how quickly will Avicel itself return to setting viscosity. It is not addressed in either of the paragraphs he just cited.

MR. BERGHOFF: I didn't mean Avicel. It's an Avicel suspension such as Nasacort AQ, such as --

THE COURT: Let me see counsel for a second.

(The following took place at sidebar.)

THE COURT: Okay. Let's see.

MR. BERGHOFF: So this is the easier one. This is talking about Nasacort AQ which includes the Avicel CL compound. It says high level. It indicates that the structure will rebuild quickly after spraying for shear. That is all. I'm having him say in general, in general terms.

MR. HURST: The question seemed to me --

THE COURT: Was a little more specific?

MR. HURST: Yes, it was.

THE COURT: So do you understand the import of his objection, why he is objecting to the question? And if you do, and you disagree, just tell me.

MR. BERGHOFF: I believe that this is just the generalization of what we will cover specifically.

MR. HURST: I'm sorry.

THE COURT: Okay.

MR. HURST: Here is what the witness will say. It sounded like he was asking how quickly will Avicel return to the setting viscosity? That was the question. And if he says something like a minute, 30 minutes -- I don't know what he is going to say but that issue itself is nowhere in any of his reports and that seemed to be what the question is designed to elicit.

MR. BERGHOFF: I disagree.

THE COURT: You disagree. Well, where is it then?

MR. BERGHOFF: That sentence is not -- he is just going to say quickly. He is not going to put a number.

THE COURT: However quickly he says it, I don't think that is the objection. It's whether he had a fair notice and fair chance.

MR. BERGHOFF: I'll go through the reports first, and then --

THE COURT: I don't want to prolong this. I am going to sustain the objection as I understand the objection to be directed to the specific question that you are asking.

MR. BERGHOFF: Okay.

THE COURT: If you want to go into the more general with him and then at some point?

MR. BERGHOFF: No, I can get to where I need to go by going to the reports.

THE COURT: All right. That's fine.

MR. BERGHOFF: I can do that. It may lengthen it.

THE COURT: Okay. We'll do it. Well, we have these Rules of Evidence that encompass them.

MR. HURST: Thank you.

THE COURT: All right.

MR. BERGHOFF: I understand. Thank you.

(End of sidebar conference.)

BY MR. BERGHOFF:

Q. **Let's turn, if we could, Dr. Prud'homme, to PTX-380. And that should be in your binder and we'll put up the front page.**

A. **Yes.**

Q. **Could you tell us what this document is?**

A. **This is a report from FMC evaluating the Nasacort AQ formulation for its rheological properties.**

Q. **And for whom was this report generated by FMC?**
A. **Dale VonBehren.**
Q. **And what company was it sent to?**
A. **It was sent to Rhone-Poulenc Rorer.**
Q. **And just in very general terms, what is the subject of this report? At what time was FMC testing?**
A. **Testing the rheology, in particular, the suitability of this formulation to act as a spray application.**
Q. **And by "this formulation," you mean Nasacort AQ?**
A. **Nasacort AQ.**

MR. BERGHOFF: Let's pull up, if we can, one of the conclusions in this report from FMC.

BY MR. BERGHOFF:

Q. **Do you see the highlighted sentence, Dr. Prud'homme: the high level of thixotropy indicates that the structure will rebuild quickly after spraying?**
A. **Yes, I see it.**
Q. **Could you tell us what that means with respect to the structure of Nasacort AQ?**
A. **The high level of thixotropy is indicating the high level of network microstructure being broken down by shear as shown in the previous slide, that it easily does that. It's easily broken down and that it rebuilds rapidly back to a gel-like state after shear -- after spraying, after shear has been applied.**

Q. **And the Nasacort AQ that has was being tested here by FMC, that includes Avicel CL 611?**

A. **Yes, it does.**

Q. **Have you reviewed the data in this report, Dr. Prud'homme, in detail?**

A. **Yes, I have.**

Q. **And does the data in this report support the conclusion that FMC reached that the structure will rebuild quickly after spraying?**

A. **Yes, I believe it does.**

MR. BERGHOFF: Let's turn to PTX-365, if we could.

BY MR. BERGHOFF:

Q. **And do you recognize this document, Dr. Prud'homme?**

A. **Yes, I do.**

Q. **And it's entitled Rheological Properties of Nasal Spray Products. Do you know for whom or by whom this report was generated?**

A. **I've been told it was generated by Hydan Technologies. That was the company formulating it or back-engineering the product for Barr.**

Q. **I'm not sure Barr was on the scene, just to be absolutely correct, yet. I'm not sure they had signed their agreement with Agis but Agis is the company that eventually licensed the product to Barr. That is your understanding?**

A. **Yes.**

Q. **And in general terms, what does this report deal with? What are they testing here?**

A. **They're testing the rheology, using many different dimensions and parameters of that, and one of the key ones is the time scale for that structure to rebuild the kinetics.**

Q. **And the time scale for what structure to rebuild? What product?**

A. **The thixotropic structure in those products that are mentioned in that topic -- table and Nasacort AQ being among them.**

Q. **And what did the Hydan report show about the recovery of structure of Nasacort AQ after shear is taken away?**

A. **This report shows structure is recovered very rapidly.**

MR. BERGHOFF: Could we look at Figure 2 in the Hydan report?

BY MR. BERGHOFF:

Q. **And we have a demonstrative exhibit that you helped us prepare for that purpose, Dr. Prud'homme. Do you see that?**

A. **Yes.**

Q. **Is this demonstrative consistent with the actual black-and-white Figure 2 in the Hydan report?**

A. **Yes, it is.**

Q. **And which color line is Nasacort AQ?**

A. **The orange-colored line, the second from the bottom.**

Q. **And what does this figure from the Hydan report tell us about the recovery of viscosity by Nasacort AQ, if anything?**

A. **This experiment is done in what is called a Hokkaido Viscometer, a different instrument than the Brookfield, a different geometry. And the material is first subjected to a high shear rate, high flow conditions from zero to 30 seconds. And we see there, the viscosity is quite low, indicating the structure was broken down. And then at 30 seconds, suddenly, this fast flow is turned off and the very slow flow is maintained, very low stress condition. And what one sees is the viscosity immediately jumps to a very high level and recovers that lost structure. It rebuilds, as shown here, extremely rapidly.**

MR. BERGHOFF: Your Honor, may I approach the screen, just to be sure I'm following where on the graph we are?

THE COURT: Sure.

BY MR. BERGHOFF:

Q. **In this portion of the orange line for Nasacort AQ, what is happening here, Dr. Prud'homme?**

THE COURT: What portion are you indicating, for

the record?

MR. BERGHOFF: It's the bottom-most portion on the left.

THE COURT: So what is that, the X or the Y axis?

MR. BERGHOFF: It's almost near zero on the Y axis and from zero to 30 on the X axis. Thank you, Your Honor.

THE WITNESS: So the Y axis is viscosity. And we see very low viscosity values under this high shear where all the tumbleweeds have been broken apart and flowing readily.

BY MR. BERGHOFF:

Q. **So this is high energy, low viscosity?**

A. **High energy, low viscosity, broken-up tumbleweed structure.**

Q. **What happens to the orange line at the 30 second mark?**

A. **At this point, instead of high shear, one goes to a very low shear, very low stresses, which I believe would mimic the as-deposited-low-stress state in the application of the spray onto a surface. And at that point, the viscosity now jumps up to a level, much higher level and it does that very rapidly.**

Q. **And by "very rapidly," how rapidly, Dr. Prud'homme?**

A. **One can see from that, that the stress is recovered in much less than 30 seconds to 90 percent of the ultimate value it attains in that experiment.**

Q. **And the Nasacort AQ that was being tested by Hydan for Agis, that, of course, includes the Avicel CL 611?**

A. **Yes.**

Q. **Let's turn to the infringement issues. You have reviewed the patents in suit, Dr. Prud'homme?**

A. **Yes, I have.**

Q. **You have reviewed the Court's ruling concerning the meaning of claim terms?**

A. **Yes, I have.**

Q. **You're familiar with Barr's ANDA product?**

A. **Yes, I am.**

Q. **And do you have an opinion as to whether it's the same as Nasacort AQ or not?**

A. **I believe the formulation is identical.**

Q. **And they both contain Avicel CL 611?**

A. **Yes, they do.**

Q. **Now, you gave a general definition for us before of thixotropy or what it means to be thixotropic. Do you understand the Court in this case has defined the meaning of the thixotropic properties in the claims?**

A. **Yes, I do.**

Q. **And do you understand that you are to apply that**

definition when assessing the issue of infringement?

A. **Yes, I do.**

MR. BERGHOFF: Can we put up the Court's order? We've marked this as PTX-360. And we're looking at the second paragraph.

BY MR. BERGHOFF:

Q. **Is this your understanding of the Court's order concerning thixotropic properties that the Court will limit the term "thixotropic" to refer to those properties described in specific claims or, in the absence of properties described in a specific claim, those properties described in the specification?**

A. **Yes, it is.**

MR. BERGHOFF: Let's turn, if we can, to Claim 26 of the '329 patent.

BY MR. BERGHOFF:

Q. **And I've put up on the screen the words from that claim that relate to thixotropic properties. They'll have the whole claim up there. And are these the only words that you will be addressing, Dr. Prud'homme, in the claim?**

A. **Yes.**

Q. **Does this claim, Claim 26, describe specific thixotropic properties?**

A. **Yes, it does.**

Q. **And where do you see that?**

MR. HURST: Objection, Your Honor.

THE COURT: Yes, sir. What is your objection?

MR. HURST: It sounds like we're having claim construction argument in terms of what -- if I can explain why?

THE COURT: You will have to do it over here a second.

MR. HURST: Okay.

(The following took place at sidebar.)

THE COURT: I'm not sure that I understand your point.

MR. HURST: Yes. This is your ruling. Now he is telling the witness to apply your ruling to Claim 26.

THE COURT: Right.

MR. HURST: Claim 26 is dependent on Claim 25. Claim 25 specifies no thixotropic properties, which means that Claim 25 requires, according to your ruling, the thixotropic properties set forth in the specification.

THE COURT: Okay.

MR. HURST: I think the argument that is being made is because Claim 26 depends on Claim 25 that the specification properties are not incorporated into 26.

THE COURT: Is that what you are attempting to adduce, evidence to support an argument consistent with that?

MR. BERGHOFF: I am making clear what the witness is assuming in terms of his testimony.

THE COURT: You understand it's a claim construction ruling.

MR. BERGHOFF: Yes, I'm not disputing that at all. No.

THE COURT: I'm just making sure for the record you that you do.

Your objection is overruled.

MR. HURST: Thank you, Your Honor.

MR. BERGHOFF: Yes.

THE COURT: Okay. Fine.

(End of sidebar conference.)

BY MR. BERGHOFF:

Q. **Does this claim describe specific thixotropic properties, Dr. Prud'homme?**

A. **Yes, it does.**

Q. **And where are those properties found?**

A. **In the I and II subsections.**

Q. **And the first I talks about the viscosity in the unsheared form?**

A. **Yes.**

Q. **And the second I talks about it in the sheared or shaken form?**

A. **Yes.**

Q. **Dr. Prud'homme, you were here for Dr. Lochhead's testimony?**

A. **Yes.**

Q. **And are you relying on his viscosity testing?**

A. **Yes, I am.**

MR. BERGHOFF: And let's put up Plaintiffs' Demonstrative Exhibit 48.

BY MR. BERGHOFF:

Q. **Does this slide accurately depict the results of Dr. Lochhead's viscosity testing on the Barr ANDA product and Nasacort AQ?**

A. **Yes, it does.**

Q. **And you're relying on that. So these are the results you are relying on from Dr. Lochhead?**

A. **Those are the results that I'm relying upon.**

Q. **And did the viscosity setting, viscosity of Barr's product as tested by Dr. Lochhead fall within the setting viscosity range set forth in Claim 26, in your opinion?**

A. **Yes, it does.**

Q. **Same question for the shear viscosity of Barr's ANDA product and the shear viscosity range set forth in Claim 26.**

A. **Yes, it does.**

Q. **Let's turn now to Claim 6 of the '573 patent. Do you recognize, Dr. Prud'homme, that this is the language from that claim that relates to thixotropic properties?**

A. **Yes, I do.**

Q. **And there are specific thixotropic properties laid out in Claim 6?**

A. **Yes, there are.**

Q. **And could you identify those for us?**

A. **Again, the first I is the viscosity of the composition in unsheared form, the next is the composition in the sheared form and the next is in the deposited form.**

Q. **Let's deal with the first two for the moment. Is your testimony the same with respect to the Barr ANDA product meeting the limitations of this claim with respect to unsheared form?**

A. **Yes, it is.**

Q. **And that's based on Dr. Lochhead's testing that we just saw?**

A. **Yes, it is.**

Q. **Is it same answer with respect to the sheared viscosity, which is roman numeral two in this claim?**

A. **Yes, it is.**

Q. **And what do you base that conclusion of infringement on?**

A. **Again, on Dr. Lochhead's rheological measurements.**

THE COURT: Counsel, perhaps this would be a good time for everyone, me included, to take a brief stretch.

(Brief recess taken.)

THE COURT: Please be seated.

Counsel, you may continue.

MR. BERGHOFF: Thank you, Your Honor.

Let's put the claim language back up from Claim 6 of the '573 patent.

BY MR. BERGHOFF:

Q. And we'll turn our attention to the third clause, Dr. Prud'homme.

A. Yes.

Q. And do you understand that the Court has a specific construction of the language in the third clause?

A. Yes, I do.

MR. BERGHOFF: Let's just be sure we have that. Can we put up the Court Order that is 360? And it's Paragraph 5, I believe. It continues on. Yes, there we go. To the next page.

BY MR. BERGHOFF:

Q. And that is the definition of this third clause that you are applying, Dr. Prud'homme, in your analysis?

A. Yes, it is.

Q. Now, Dr. Prud'homme, can you, as far as you know, measure the deposited viscosity directly in the nose with a Brookfield viscometer?

A. So in the nose, it cannot be measured. The

Brookfield viscometer is a physical instrument that certainly can't be applied in the nose.

Q. **And why is that?**

A. **It's physically too large to be inserted into the nose and to have the volumes of fluid that are specified by the Brookfield manual.**

Q. **Would a person of ordinary skill in the art know that?**

A. **Yes.**

Q. **Do you have an opinion as to whether the viscosity of Barr's ANDA product would return to its unsheared viscosity following deposition in the nose?**

A. **It's my interpretation of what this means is that that the Avicel structure rebuilds that tumbleweed network and it rebuilds it real quickly. In that rebuilt form, that tumbleweed structure would have the viscosity of 400-to-800 centipoise given the only technique that the patent gives for doing the measurement, which is an at rest measurement.**

Q. **And what is the basis of your opinion that in the nose, in deposited form, the material of Barr's ANDA product would return to this unsheared viscosity range of 400 to 800?**

A. **It comes from my understanding of thixotropic materials in general, the Avicel in particular, my interactions with FMC, the Hydan data that we looked at that**

shows the rapid rebuilding of structure and the FMC cover letter as well as data showing that it would very rapidly rebuild.

MR. BERGHOFF: Now, let's just return, if we could, to the Hydan data. If we could put back up that Figure 2 from the Hydan report that we had up before, Plaintiffs' Demonstrative Exhibit 43. There we go. Great.

BY MR. BERGHOFF:

Q. Do you have an opinion as to whether the data here relates to what happens to nasal spray when it's deposited in the nose?

A. Yes. The first part of that experiment, very high shear rates represents the spraying process. The injection of the liquid out of the aerosol container, the formation of small droplets, all of that happens at high stresses or shear rates when the structure is broken down as shown on the left.

And then we see a very rapid regain of that --

MR. HURST: Objection.

THE COURT: Basis, counsel.

MR. HURST: He is going outside the scope of his expert report on the second part, which he is about to go to, which is whether that line relates to which --

THE COURT: Which line?

MR. HURST: The at 30 seconds, when it goes up

to a higher level. The question --

THE COURT: What color is the line?

MR. HURST: I forget which one is Nasacort.

MR. BERGHOFF: It's the orange one.

MR. HURST: The orange line.

THE COURT: All right.

MR. HURST: The question is whether that relates to what happens in the nasal cavity. And he has offered to no opinion on that subject, Your Honor.

THE COURT: Is that accurate, counsel?

MR. BERGHOFF: No, I don't believe so. But let's look at the report.

He did talk about -- should we come up here? It's up to you, Your Honor.

THE COURT: Yes.

(The following took place at sidebar.)

MR. BERGHOFF: He clearly did express an opinion that in deposited and relatively unstressed form, that is what it is when it's in the nose. And that is exactly what he has already gone through on the Hydan report. So I think we're very fair here.

MR. HURST: When he explained what he meant by this, he explained I do not have any expertise in what actually happens.

THE COURT: You may cross-examine him.

MR. HURST: Okay. Fair enough.

(End of sidebar conference.)

BY MR. BERGHOFF:

Q. **Your explanation was interrupted in midstream.**

A. **Yes, it was. Do you want the question read back or would you want --**

MR. BERGHOFF: Let me try it again.

THE COURT: Okay.

BY MR. BERGHOFF:

Q. **What about the data on Figure 2 relates to what happens to Nasacort AQ when it is deposited in the nose?**

A. **So the left hand, from zero to 30 seconds, represents the high stress condition, when the tumbleweed structure is broken down, the viscosity is very low. Then once deposited, those aerosol droplets landing on a surface, that is a very low stress condition, and that orange curve shows what happens to the viscosity, microstructure of that under that very low stress condition. It rapidly rebuilds to a much higher level.**

Q. **Does the patent say anything about what condition the suspension is in when it's deposited in the nose, whether it's stressed, unstressed?**

A. **It says that it's in a relatively unstressed condition or unstressed conditions.**

MR. BERGHOFF: May we have the exact language

here from PTX-1, Column 4?

BY MR. BERGHOFF:

Q. **Is this the language you were referring to?**

A. **Yes, deposited and relatively unstressed form. So in a deposited form, it's relatively unstressed.**

MR. BERGHOFF: And then if we can go back to the Hydan chart.

BY MR. BERGHOFF:

Q. **What happens to the material when the stress is removed, when it is relatively unstressed in this data?**

A. **So this tumbleweed network structure rebuilds and the viscosity rebuilds to form a gel-like material.**

Q. **And how does that support your opinion that the viscosity of the deposited material, Barr's ANDA product, Nasacort AQ in the nose would return to its setting viscosity?**

THE COURT: I need to ask counsel a question. Could I see you?

(The following took place at sidebar.)

THE COURT: There has been a lot of discussion about the patented formulation of Nasacort. And I understand that from the standpoint of context and giving me background. On one of the demonstratives, just before we broke, there were testing results from the Barr product. Below that were testing results from the Nasacort product.

I know I have to understand how infringement is adduced and established, but why is there so much continuing conversation about Nasacort?

MR. BERGHOFF: We can stop that.

THE COURT: I would appreciate it. I'm going to do my job and compare the claims to the accused product. Okay?

I don't know why this isn't enjoying objections. Is there some strategy? And maybe it's strategic, I don't know. And I don't want to put you on the spot but it's helpful for a jurist who has to sit here and listen to these complex matters when the lawyer is aware.

MR. HURST: I understand.

THE COURT: Okay.

(End of sidebar conference.)

MR. BERGHOFF: May I start again on that question?

THE COURT: Yes.

MR. BERGHOFF: Thank you, Your Honor.

BY MR. BERGHOFF:

Q. **Dr. Prud'homme, how does the data related to the Hydan report support or relate to your opinion that viscosity of the Barr ANDA product, when deposited in the nose, will return to its setting viscosity of 400-to-800 centipoise?**

A. **If I'm asked the question what are the properties of the material, and let's say it's in a small vial and I say what is the property of that material, I can measure that material in a different geometry as long as it's the same material and tell you what property of that is in some small vial, if that vial was behind a small screen or something like that.**

So measuring the properties doesn't necessarily mean you have to do the measurement in that particular vial or container. So, to me, the distinction is an important one. We can measure the properties of the material in a viscometer. And if that material is the same material that is in some other location, I can still measure the properties of that material. To me, as a scientist, that is legitimate. That is how I do science.

Q. **But you are not here holding yourself out as an expert on the nose or nasal anatomy?**

A. **No, I'm not. I'm saying, therefore, this experiment, which is not done in the nose, it's about this material which I believe in the nose would reflect these properties and these kinetics.**

Q. **Do you have an opinion, Dr. Prud'homme, as to whether, when the Barr ANDA product is deposited in the nose, it would return to a relatively high viscosity?**

A. **Again, those materials are based on Avicel, the**

Avicel material. This data showing that it returns rapidly to a relatively high value as shown by the orange line; the FMC experiments and conclusions, those researchers who work with Avicel all the time saying it will return to its thixotropic nature means it will return very rapidly to that state; all of those things lead me to believe that in the nose, it will return to this relatively high thixotropic state.

Q. One last question. Dr. Prud'homme, what is your opinion as to whether the Barr ANDA product, when deposited in the nose, forms a viscous composition?

A. Yes. All of these materials, as shown in that data, are viscous materials.

MR. BERGHOFF: No further questions.

THE COURT: Thank you, counsel. You may cross-examine.

MR. HURST: Thank you, Your Honor.

CROSS-EXAMINATION

BY MR. HURST:

Q. Good morning, Dr. Prud'homme. How are you?

A. Good morning. I'm very fine.

Q. I'd like to start by talking about the claims themselves, in particular to roman numeral three on the claims.

MR. HURST: Can we put up Defendant's Exhibit 7

at 10, Claim 5.

Can you put all three roman numerals up just to make it simple and readable?

BY MR. HURST:

Q. So, Dr. Prud'homme, you're here to talk about the third element of the claims here, roman numeral three, and whether Barr's product returns to a viscosity of 400-to-800 centipoise on the mucosal surfaces. Right?

A. Part of it, yes.

Q. Now, this claim refers specifically to mucosal surfaces. Do you see that?

A. Yes, I do.

Q. You are not an expert on mucosal surfaces, are you?

A. I'm not an expert on mucosal surface.

Q. And you are not an expert on the various nasal secretions that occur in the nose. Correct?

A. No, I benefitted from listening to the deposition yesterday on that topic.

Q. And you have done no analysis on how nasal fluids might impact the viscosity of Barr's product in the nasal cavity. Correct?

A. Actually, yesterday, I did the calculations back in the court after listening to Michael's calculations.

Q. Can I --

A. So this is --

Q. **If you are going to talk about a calculation you did yesterday, then I'm going to rephrase my question.**

A. **Okay. Please do.**

Q. **Prior to yesterday, is it fair to say that you have done no analysis on how nasal fluids impact the viscosity of Barr's product in deposited form? You have done no analysis?**

A. **Prior to yesterday and seeing the data presented by the expert witness yesterday, I had not done any calculations.**

Q. **Okay. And you're not an expert on ciliary forces within the nasal cavity either, are you?**

A. **I am not an expert in that.**

Q. **And you have done no analysis, have you, on how ciliary forces within the nasal cavity impact the viscosity one way or another of Barr's product. Correct?**

A. **After seeing the videos yesterday, I draw conclusions from those videos relating to the area of rheological expertise.**

Q. **I'm going to rephrase my question.**

A. **Okay.**

Q. **Before yesterday, is it true that you conducted no analysis on how ciliary forces within the nasal cavity would impact the viscosity of Barr's product and whether, in fact, it meets roman numeral three?**

A. **That is true.**

Q. **Now, you do understand, of course, that it's hotter in the nasal cavity than it is in typical laboratory settings. Correct?**

A. **I learned that yesterday. And will that be in or out of things I can comment on?**

Q. **As long as you are going to be offering opinions that are in your expert reports and we've had an opportunity to depose you on, I'm happy to hear them. But opinions that were developed yesterday, I'd rather not. Okay?**

Now, it is true, is it not --

THE COURT: I wonder. It's an interesting dilemma, because both sides have agreed to permit experts to remain in the courtroom. A trial is a living, breathing thing, and stuff happens that is unexpected. We have experts, people who are acknowledged experts within their fields. Brilliant scientists. Why should they be precluded from formulating views based upon what they're hearing from other experts? I don't know.

MR. HURST: That's a fair question, Your Honor. But obviously it would be outside the scope of the expert reports, but more particularly here, this expert has admitted to a lack of expertise on the environment within the nasal cavity and, therefore, it would not necessarily be helpful to the Court in my view.

THE COURT: Fair enough.

MR. BERGHOFF: Subject to my perhaps revisiting this when it's my turn.

THE COURT: All right. I think I have opened the box. Okay.

BY MR. HURST:

Q. **Let's make clear. You are not an expert on nasal secretions within the nasal cavity. Correct?**

A. **No. That is why I listened with interest to the expert witness yesterday.**

Q. **And you are not an expert in ciliary forces within the nasal cavity. Correct?**

A. **That's why I found his video so fascinating.**

Q. **And as far as you know, nobody in this case tested Barr's product in any model that was designed to mimic the conditions within the nasal cavity. Correct?**

A. **I believe that the rheological measurements of the structure of the Nasacort AQ are reasonably mimicked in the Brookfield viscosity measurements which is why it's reflected in the claims of the patent.**

Q. **For instance, it's hotter in the nasal cavity. Right? It's about 30 degrees hotter than room temperature. Correct?**

A. **I defer to your expertise.**

Q. **And there is no testing by anybody from Aventis on**

the recovery rate of Barr's product at 98.6 degrees. Correct?

A. **That is correct.**

Q. **And there is no testing from Aventis on the recovery rate here for roman numeral three, Claim 5? There is no testing from Aventis on the recovery rate and viscosity of Barr's product when nasal fluids are added to it. Correct?**

A. **That's correct.**

Q. **And there is no testing from anybody at Aventis on the recovery rate of Barr's product, looking again at roman numeral three, when ciliary forces are introduced into the mix. Correct?**

A. **They have not done that. I don't believe those forces are significant.**

Q. **Right. And the temperature of the testing probably would have been easy to do. Right?**

A. **I believe temperature has essentially zero effect on the rheology of these fluids.**

MR. HURST: Can we pull up Page 228 of Dr. Prud'homme's deposition?

May I approach, Your Honor?

THE COURT: Yes, you may.

BY MR. HURST:

Q. **Do you need this or is the screen fine?**

A. **And this point the screen will be fine. Thank you.**

Q. **Okay. At the top here:**

"Question: First, you agree that difference in temperature can have an effect on viscosity?

"Answer: For what material and over what temperature range?

"Question: For the accused Barr product over the temperature range of room temperature to nose temperature?

"Answer: There may be effects due to temperature changes.

"Question: You just don't know one way or the other whether there are any in this case. Right?

"Answer: I have not seen measurements on materials with different temperatures on the Barr material or the Aventis material."

Did you give those answers to those questions, sir?

A. **Absolutely correct.**

Q. **Okay.**

A. **But I had that experience with vis-a-vis Avicel type materials done at different type of materials and for these type of materials, there is very little temperature dependence on the Avicel material.**

Q. **In fact, in your expert report, you mentioned none of the temperature-related experiments that you just referred**

to. Correct?
A. That is correct.
Q. Okay. Now, let's go back to number three. I want to direct your attention to this particular prong of the claims, and in particular, Barr's product. And here is my question:
Sir, you have no opinion, one way or the other, on whether Barr's nasal spray would return to its unsheared viscosity after being deposited in the nose. Correct?
A. I'm not an expert in the nose. I have opinions on whether the material itself would regain structure and under what conditions that would occur.
Q. But my question is you don't know, one way or another, whether Barr's product would return to its unsheared viscosity after being deposited in the nose, do you?
A. My expectation again, as I went through this discussion about if I have a material in one location and I measure the same material in another location, would it be similar or different if there were not forces that changed that material, then my experience would tell me that the Nasacort material will retain or the Barr material will, once again, regain those characteristics of the unsheared material.
MR. HURST: Can we go to your deposition at Page

189, spilling over to 190, Line 18.

BY MR. HURST:

Q. **"Question: You agree, though that it would -- you don't know one way or the other in the nose whether once applied the shear returns to unsheared for any of the nasal sprays that we are talking about today. Right?**

"Answer: I am not an expert in nasal passages and have no opinion in that area.

"Question: Have you done any analysis or do you have any opinion about whether or not the sheared nasal spray returns to a thicker, more viscous material before the chance of clearing from the nose because of how the nose works?

"Answer: I am not an expert in the nasal part of that question or in clearance rates or anything like that, so I would not know."

Did you give those answers to those questions, sir?

A. **Absolutely, yes.**

Q. **Let's take a look now at the two reports that your counsel asked you to review during your direct examination.**

First let's take a look at Plaintiff's Exhibit 380.

This is an FMC report relating to testing with Barr's product. Is that right -- I am sorry, this is with

Nasacort?

A. **Yes, it is.**

Q. **This is not testing with Barr's product. Correct?**

A. **This is testing with Nasacort.**

Q. **Now, the testing in this report, am I correct that there was no effort to try to mimic the conditions in the nasal cavity? Is that true?**

A. **That is true.**

Q. **There was no testing at body temperature in this report. Correct?**

A. **It was done at ambient temperature.**

Q. **And there was no effort to try to introduce fluids into the formulation to mimic the action of nasal fluids being introduced in the system. Correct?**

A. **I don't know if nasal fluids would be introduced into the system.**

Q. **And there was no effort to try and introduce the level of shearing forces that might come from cilia beating a thousand times a minute. True?**

A. **Based on discussion yesterday I don't believe those forces would be significant.**

Q. **But my question is, there is nothing in the FMC report doing any testing on that issue?**

A. **You were importing the idea of cilia forces. There is nothing in here that relates to cilia forces.**

Q. That's my question.

Now, if we go to the Hydan report, which is Defendant's Exhibit 76, it's just another version -- it's the same document, different number, this is another document that you looked up with counsel. Correct?

A. Yes.

Q. Now, again, this particular testing, this was not testing with Barr's product. Right?

A. No. This was testing with other commercial products.

Q. Am I correct, then, that both of the reports that you talked about for your opinion, the FMC report and the Hydan report, they were both testing with Nasacort. Correct?

A. That is correct.

Q. Not Barr's product. Right?

A. Barr's product is an identical composition to the Nasacort which was tested, correct.

Q. You did see earlier the viscosity testing that Dr. Lockhead had done, right, to show different sheared viscosities for Nasacort versus Barr? You saw that. Right?

A. I saw that data.

Q. Now, on this Hydan report, again -- and I won't belabor it -- but there is no effort when they are testing Nasacort to mimic the conditions in the nasal cavity. Correct?

A. There are no efforts to do that.

Q. **Now, also, for both of these reports that you looked at, I didn't hear you mention the range of 400 to 800 centipoise. Did you?**

A. **I did not.**

Q. **Now, let's go back to the claim, Claim 5, III, do you see where it says that the return has to be the 400 to 800 centipoise?**

A. **Yes.**

Q. **And the reason, when you talked about these two reports, you didn't mention 400 to 800 centipoise is because neither report mentions 400 to 800 centipoise. Correct?**

A. **No.**

Q. **They do not. Right?**

A. **They do not mention that.**

Q. **Now, I just want to spend a little time looking at this. In the Hydan report, which is Defendant's Exhibit 76, I want to take a look at Page 5 of this exhibit. Now, this is the exhibit you were relying on to argue that recovery to a setting viscosity happens rapidly. Right?**

A. **Part of the evidence, yes.**

Q. **I just want to make sure that I understand the timing of this. Okay. The timing for these tests is actually only 120 seconds. Right?**

A. **That is true.**

Q. **And so one of the things, if a product -- this is**

pretty violent shearing, from 0 to 30 seconds, that is fairly violent shearing?

A. **It is a hundred reciprocal seconds, yes.**

Q. **As soon as the violent shearing is removed, the viscosity jumps up. Right?**

A. **Yes, it does.**

Q. **But this doesn't mean that the material returned to its at-rest setting viscosity in 30 seconds, does it?**

A. **I believe it does indicate that.**

Q. **Let's talk about that. So your view is that after only 30 seconds, these materials in question return to their setting viscosity? That's your view?**

A. **The microstructure -- you have introduced the term setting viscosity. What I infer from that is the microstructure of this Avicel material returns to a highly structured interconnected state.**

Q. **I am talking about the viscosity required by the patent, 400 to 800 centipoise. That is what I am talking about. Is it your view that in 30 seconds these materials in question return to a viscosity of 400 to 800 centipoise?**

A. **That number 400 to 800 centipoise is defined by a very specific set of experimental protocols listed in the patent and relied upon by, or conducted by Bob Lockhead.**

Q. **Let's take a look at Dr. Lockhead's experiments. Let me put up Dr. Lockhead's report, which is Defense Exhibit**

362. We will go to Page 9. Why don't we pull out Sample 3.

Now, you understand that this testing -- let's orient ourselves here. This is testing with Barr's actual product. Right?

A. **Yes.**

Q. **Unlike the Hydan and FMC reports. Right?**

A. **Yes.**

Q. **And the setting viscosity that Dr. Lockhead found was about 600. Right?**

A. **Yes.**

Q. **And then he tests shear viscosity. Right?**

A. **Yes.**

Q. **And he takes three measurements over the course of about two minutes. Right?**

A. **Yes.**

Q. **And at the end of the two minutes, even at the end of the two minutes, am I correct that the -- at the end of the two minutes the reading is 96.8. Right?**

A. **Yes.**

Q. **And the setting viscosity is about 600. Right?**

A. **Yes.**

Q. **So at the end of two minutes, am I correct that the setting viscosity remains about six times as high as the shear viscosity?**

A. **Approximately correct.**

Q. **Now, in terms of measuring how long it takes Barr's product to return to setting viscosity, I just want to set aside the nasal viscosity for one second. Even on a tabletop, Dr. Lockhead could have measured how long it takes to get back up to 600, or even to 400, as the claims say, just by testing again a half-hour later. Correct?**

A. **Not quite. This measurement is to define two viscosity values the patent lays out. I have written several patents. One wants to put in specific tests so one can know whether one is violating the patent or not.**

They define these two tests with what they have called, I believe in the patent it says for simplicity or for convenience, they are going to define these as two words, setting viscosity and shear viscosity. That's what those are. That is what the patent is defining as thixotropy or this is what we patented.

There are many other ways to measure the kinetics of re-healing. I believe the Barr and FMC are better ways of measuring how fast those transitions occur, and that this -- there is nothing in the patent that defines how fast this transition occurs.

Q. **Just taking my question for one second. If we wanted to find out quickly Barr's product returns to its setting viscosity even on the tabletop, without nasal fluids, without ciliary action, just on the tabletop, all Aventis**

had to do was test again after 30 minutes. Right?
A. The Brookfield Viscometer, because of that geometry, and concentrating stress near the spindle, and operating this measurement at a high speed, 30 RPMs, disrupts structure significantly. It allows you to do this measurement they have defined, but it is not the best measurement to look at how fast something evolves, in my opinion.
Q. All I am saying is they could have let it rest completely for 30 minutes or an hour and then test it again to see if over that entire period Barr's product would return up to 400 to 800 centipoise as required by III. Correct?
A. One could do that experiment.
Q. And nobody decided to do that. Right?
A. I did no measurements and was not in the decision loop for measurements.
Q. So you did no testing in this case?
A. I did no testing in this case.
Q. Just one more line of examination, a few questions.
Can we put up, please, DX-23? Defendant's Exhibit 23.
Can we highlight, please, the first part of this. I talked to Dr. Lockhead about this testing. Right?
A. Yes.

Q. **And why don't we just make sure, I don't even want to characterize it, it is viscosity of Nasacort AQ versus Beconase. Right?**

A. **Yes.**

Q. **What Aventis did was test, as they say, the viscosity of their product versus Beconase and Vancenase to see if they return to their unshaken state at equal times. Right?**

A. **That's what that says, yes.**

Q. **So this is testing, the kind of testing that I was talking about, waiting, seeing how long a fluid takes to return to its setting viscosity on the tabletop. Right? It's that kind of testing?**

A. **It appears to be, yes.**

Q. **Now, when you signed your expert report in this case, your opening report on III of that claim, am I correct that you did not consider any of this testing with the Nasacort product and how long it takes to return to its setting viscosity?**

A. **I would have to look at in what stage of these, my reports and rebuttals this document was considered. I don't recall when that was.**

Q. **Why don't we take a look at your opening report, Defendant's Exhibit 366. If you look at Page 3, if it helps, it's on the screen.**

A. **Thank you.**

Q. It spills over to the next couple of pages. We list a lot of the things that you considered in arriving at your opinion about whether Barr's product returns to 400 to 800 centipoise in the half-hour or so it remains in the nasal cavity. Right?

A. Right.

Q. Now, you didn't consider this Aventis testing that took place over the course of five days in forming your opinion with respect to infringement. Correct?

A. If that's not listed among here of the things that I have looked at, then I had not looked at that at that point.

Q. You can confirm for yourself, it is a couple of pages. You are not going to see it there, Doctor.

A. I take your word for it.

MR. HURST: All right. Thank you, Doctor. I have no further questions at this stage.

THE COURT: Redirect.

REDIRECT EXAMINATION

BY MR. BERGHOFF:

Q. Dr. Prud'homme, if I can just refer to it as the tabletop experiment that Barr's counsel keeps referring to, where we just let I guess some Barr ANDA material sit on the tabletop for a period of time and then we measure it with the Brookfield Viscometer, what's your opinion as to the relevance of that with respect to the viscosity of the Barr

product after it's deposited in the nose?

A. **I believe that the recovery of the microstructure in that sprayed material is very rapid, as shown by the Hydan data, as shown by the FMC report and FMC comments and the fact that FMC anticipated using this as a spray on skin. That's what they thought this test was about.**

I have been involved with FMC in those sorts of spray applications. You need something that sticks on the skin, has enough thixotropic structure, doesn't drip off. So you needed something that would rebuild quickly. That is a fundamental characteristic of Avicel, that it rebuilds structure quickly. So I believe that this deposit in the nose material rebuilds structure very quickly.

Q. **Is it your opinion that the Hydan report and the FMC report are more or less relevant than this hypothetical tabletop experiment?**

A. **I believe they are much more relevant, because in this tabletop experiment, one is taking this material, and then when one dips the Brookfield Spindle into that, one has concentrated all the stresses in that measurement, and is doing that measurement at a very high stress level. So the measurement itself is changing the structure. So the measurement influences the results.**

I believe in that case that it makes it less germane to the question of the time scales, because the

measurement is perturbing those time scales, I believe. And that doesn't occur in the Hydan instrument or in the FMC instrument, which is two very thin gaps.

So the stress is uniform in that very small volume, and it's imposing a much more regular stress-energy distribution on those materials. That occurs when you take that small spindle and put it in the large beaker.

Q. Since you referred to the equipment, perhaps, could we just put up a diagram, just to show the Court, it's Plaintiffs' Demonstrative Exhibit 38. Did you help prepare this, Dr. Prud'homme?

A. To the left is the Brookfield LVT geometry drawn to scale. The bottle, this low-form bottle that has been described, it is three and a half inches in diameter, you have a very large volume of liquid.

You dip that small disk on a shaft into that and you begin turning.

So most of the energy is being put in right near that turning object, and there is very little energy putting in this the greater volume of that liquid.

In contrast, the device used in the, geometry used by FMC and Hydan, shown to the right, there you have a, it's actually a very shallow cone and a plate. The blue liquid is that thin fill of liquid confined between the cone and the plate. It sees a very uniform stress field as

opposed to the very un-uniform stress field shown for the Brookfield.

Therefore, it is much better for looking at things like kinetics and for looking at things which have very sensitive structures, as this does.

However, the Brookfield instrument is a very fine instrument. It's the instrument that is in all the quality control labs.

THE COURT: Do you have a question?

MR. HURST: Your Honor, this is beyond the scope of cross. It is a prepared demonstrative exhibit that was obviously prepared in advance. I did not ask anything about the cone and plate device at all.

MR. BERGHOFF: This is the device in the FMC report and the Hydan report that we have been talking about.

THE COURT: I understand that. I will give you a little leeway. But you are beyond the scope of his cross-exam.

MR. BERGHOFF: I am finished. He mentioned the apparatus. I just wanted Your Honor to see it, that's all.

BY MR. BERGHOFF:

Q. **Dr. Prud'homme, I am going to focus my question very pointedly on your opinion as of today, not as of yesterday or two days ago.**

What is your opinion today as to the effect of

the cilia in the nose, based on the testimony you heard in court yesterday, on the viscosity of Barr's ANDA product when deposited in the nose?

MR. HURST: Objection. That's outside the scope of the expert reports. He could have talked to the same experts.

(The following took place at sidebar.)

THE COURT: He could have talked with the same experts.

MR. HURST: He could have talked with the very same experts, they are Aventis's experts, and put all of these opinions in his opening expert report. I think counsel would acknowledge, these opinions are nowhere in his expert report. I didn't get to depose him on any of these issues. I, in fact, have an expert to address how the nasal cavity will impact viscosity and fluids. The other side did not have one and I should not be forced to --

MR. BERGHOFF: I believe counsel has opened the door several times in this examination to the effect of cilia on the viscosity of material in the deposited nose. I think this is fair.

THE COURT: Overruled.

(End of sidebar conference.)

BY MR. BERGHOFF:

Q. **Dr. Prud'homme, do you need the question read back,**

or are you still with us?

A. **I am still with you.**

The answer to the question is, yesterday there was a beautiful video presented of the ciliary motion. And the expert testimony, which I am not an expert in that area, but the testimony was given by Michael, showing that the mucus layer is transported on top of that ciliary motion. And he had a series of marker spheres, dots, on top of that. And they moved uniformly in sort of a marching array across that mucosal layer as it was deposited.

The best analogy, I thought about this last night, is of a moving runway at the Philadelphia Airport. So in the moving runway you have lots of wheels underneath that are moving like mad to make the belt move. When we stand on that belt, our shoes aren't ripped apart moving around. It is conveying our shoes, conveying us, down the belt, without any disruption of ourselves.

So underlying ciliary motion, if it is merely moving that mucosal layer, is not necessarily disrupting the structure Avicel.

That expert testimony yesterday would indicate to me the ciliary motion has no effect on the microstructure of Avicel.

The other calculation I did yesterday was, because it was brought up by Barr's attorneys, would there

be dilution, that is, would liquid from the mucosal layer dilute the Avicel. That is the statement they were making. So I then did a calculation, it turns out, a calculation of the tendency of a liquid to draw water in, which is based on osmotic pressure --

MR. HURST: Your Honor --

THE COURT: I will give you another chance at him. Sit down.

THE WITNESS: So it turns out that the Avicel material has about five percent dextrose. Dextrose is added as a sugar to make it isotonic, so that it doesn't dry out membranes nor saturate membranes.

So it is equivalent osmotic pressure to biological fluids, to the mucosal fluids. So there is no tendency of that mucosal fluid to want dilute the Avicel because they are both at the same water-loving tendency.

Therefore, I would not expect dilution of a material which has a microstructured network and heal stress, is gel-like, like Avicel is.

MR. BERGHOFF: No further questions.

THE COURT: I will give you another round.

RECROSS-EXAMINATION

BY MR. HURST:

Q. The calculations that you have just discussed, did you write them down?

A. **Yes, I did.**
Q. **And did anyone give me those calculations before today, as far as you know?**
A. **As far as I know, no.**
Q. **The ciliary action that we have been discussing during this proceeding, we asked you those same questions at your deposition, didn't we?**
A. **Absolutely.**
Q. **And these experts yesterday that got up and showed that video of the ciliary action, they were experts from Aventis. Right?**
A. **For the Aventis side, correct.**
Q. **From the Aventis side, yes.**

Did you make any effort before last night to try to determine in any way, shape or form how the environment of the nasal cavity, the nasal fluids, the ciliary forces, impacted, would impact the viscosity of Barr's product while in the nose?
A. **No. Until seeing that data, that was not my area of expertise. I have an area of expertise in polymer microstructure. When I saw that data, it informs what I already know about microstructure.**
Q. **So this is a brand-new opinion from last night you are talking about?**
A. **If I had not seen that video, I would not have this**

opinion.

Q. **Do you know why Aventis attorneys never showed you that video until you saw it in court yesterday?**

A. **I am not privileged to that information.**

Q. **Do you know why Aventis attorneys never asked you to run a calculation about the mixing between nasal fluids and Barr's product until last night?**

A. **They didn't ask me to do this. I did this sitting in the back of the Court, when I heard a series of questions about wouldn't the mucosal fluid dilute. I was not asked to do that calculation. I was sitting having an enjoyable day in the back of the Court.**

Q. **They actually never asked you to do the analysis?**

A. **As a scientist, these are things I love to do.**

THE COURT: You know who asked him? You asked him.

MR. HURST: Thank you. I have no further questions.

THE COURT: Did you have anything further for the witness?

MR. BERGHOFF: No, Your Honor.

(Witness excused.)

THE COURT: Indirectly, counsel. You.

MR. HURST: I know, I understand the ruling.

THE COURT: And I accept your exception to the

ruling. But the ruling is the ruling.

Your next witness.

MR. BERGHOFF: Mr. Rich will handle our next witness, Your Honor.

THE COURT: We will take this until 12:30 and take 45 minutes for lunch.

MR. RICH: Your Honor, if we could beg the Court's indulgence, we would like to move some things around and set up some charts.

(Pause.)

MR. RICH: Your Honor, perhaps before we block off the entryway, I can call Dr. Meltzer to the stand.

THE COURT: This is going to block?

MR. RICH: I fear that it might block the easy pathway.

THE COURT: You know, let's just use this as a logical time to take an earlier break than I anticipated. We'll come back at 1:00 o'clock.

(Luncheon recess taken.)

THE COURT: Please be seated.

All right. We're ready for our witness.

MR. RICH: Yes, Your Honor. We'd like to call Dr. Eli Meltzer.

THE COURT: Okay.

- - -

PLAINTIFFS' TESTIMONY

... DR. ELI MELTZER, having been placed under oath at 1:03 p.m. as a witness, was examined and testified as follows ....

- - -

DIRECT EXAMINATION

BY MR. RICH:

Q. **Good afternoon, Dr. Meltzer.**

A. **Good afternoon.**

Q. **You're a physician; correct?**

THE COURT: Are the binders here for the doctor?

MR. RICH: Thank you, Your Honor. Might I approach the witness?

THE COURT: Yes, please.

(Binders passed forward.)

BY MR. RICH:

Q. **Dr. Meltzer, you're a physician?**

A. **Yes, I am.**

Q. **Could you describe your practice for us?**

A. **For the last 40 years, I've been taking care of patients. I do clinical care.**

For the last 30 years, I've been doing clinical research, seeing new medications and seeing if we can find better therapies for patients than ones we have.

I also have been involved in teaching for many

years. We have students from the university coming over, residents and fellows rotate through the office. And I've lectured regionally, nationally, internationally for many years, and then I consult. I do many pharmaceutical consultancies.

MR. RICH: Perhaps it would help to have his CV up, if we could.

BY MR. RICH:

Q. And you practice at the Allergy and Asthma Medical Group and Research Center?

A. Correct, in San Diego.

Q. Thank you. In your clinical work, how many patients have you treated?

A. I've never kept count. It's thousands. Many thousands.

Q. Are you board certified in any specialities?

A. I'm board certified in pediatrics and allergy and immunology.

Q. Have you written on the subject of allergies and respiratory diseases?

A. I have roughly 500 publications between abstracts and manuscripts and book chapters.

Q. And those are listed in the CV, which is in your binder as Plaintiffs' Exhibit 369.

A. It's listed. It's not up-to-date, but it's up to

2007, yes.

Q. **So it's only incomplete in that you have done more work since then?**

A. **Correct.**

Q. **Now, you said teaching and lecturing are part of what you do. How many speeches or presentations on allergy or respiratory disease have you done?**

A. **Unrelated to the teaching we do in the clinic, I've had hundreds, probably 500-plus formal presentations in different locations around the world.**

Q. **And those are also listed in your CV?**

A. **They are.**

Q. **You said as well that clinical research is part of what you do. How many clinical trials for allergy or respiratory disease drugs have you taken part in?**

A. **600-plus.**

Q. **And, again, those are listed in your CV?**

A. **They are.**

Q. **Now, if you could turn to Clinical Trial No. 554 on your CV.**

A. **(Witness complies.)**

Q. **Could you tell me what that clinical trial was?**

A. **This was a clinical trial, the sponsor was Clay-Park, which I understand is a subsidiary of Perrigo, looking at the bioequivalence of triamcinolone acetonide nasal spray, a**

generic compound, compared with Nasacort, the innovative product in terms of bioequivalence.

Q. You also mentioned consulting work. For which companies in the allergy field have you consulted?

A. Probably all of them. The ones I would highlight would the ones that have to do with internasal corticosteroids. And they include, at different points in time: AstraZeneca, Murrow (phonetic), which is now no longer in existence, Sanofi-Aventis, Schering-Plough, GlaxoSmithKline.

Q. Are there any internasal corticosteroid drugs that you haven't consulted on?

A. No.

Q. And just to be clear, you're familiar with those drugs from your work treating patients as well?

A. Absolutely.

Q. Can you tell me what your educational background is?

A. I went to the University of Pennsylvania where I received my bachelor of arts degree.

And then medical school at Jefferson Medical College.

I did my internship in Pediatrics at Michael Reese Hospital in Chicago.

My residency was back in Philadelphia at St. Christopher's Hospital for Children.

And my fellowship in Allergy Immunology in Denver at the National Jewish Medical and Research Center in the University of Colorado.

Q. **And are you on the faculty of any academic institutions?**

A. **I'm Clinical Professor of Pediatrics at the University of California in San Diego; and Past Chief of the Division of Allergy at Children's Hospital, which is the pediatric affiliate at the university.**

Q. **Now, have you ever advised the U.S. Food and Drug Administration?**

A. **I served on the Pulmonary Allergy Advisory Board for several years. They have invited people. We rotate in and rotate out after several years.**

Q. **Have you ever advised the World Health Organization?**

A. **The World Health Organization develops initiatives and initiatives that I have served on, including what they call the ARIA guidelines, the Allergic Rhinitis Impact on Asthma and Inner Airways. Those are still ongoing at this point.**

Q. **Finally, on this topic, have you received honors for your work on allergy and respiratory diseases?**

A. **I belong to three national societies: The American Academy of Pediatrics. I received the Distinguished Service Award. The American Academy of Allergy Asthma Immunology**

Distinguished Clinician Award. The American College of Allergy Asthma Immunology Distinguished Fellow Award.

MR. RICH: Your Honor, at this time, we would like to proffer Dr. Meltzer as an expert in allergies and their treatment, including specifically intranasal and steroid sprays.

MR. GRACEY: No objection.

THE COURT: The doctor is accepted.

BY MR. RICH:

Q. I'd like to turn to allergic rhinitis then. Can you tell me what allergic rhinitis is? And we have a slide to assist me.

A. Allergic rhinitis is really an abnormal response by people to normal things that we all breathe. All of us have to breathe. We need oxygen. But along with the oxygen comes everything else that floats in the air. And on this particular diagram, you can see an example which would be pollen. Ragweed is big in the East, not so much in California. It could be a cat dander. It could be a dust particle.

And when we breathe in these particles, our immune system processes them. And we process them through certain immune cells: lymphocytes, including what we call T lymphocytes. And if you are predisposed genetically to make an abnormal response to these normal substances, these T

cells instruct plasma cells to make an abnormal antibody.

All of us make antibodies called G types, A types and D types, but allergic people make the extra antibody called the E antibody. So what differentiates normal from allergic people is whether you make the E antibody. What you make the antibody to is what you are allergic to. And when you meet up with the thing you made the E antibody to, it triggers a reaction and that reaction is called the allergic reaction. And that releases from cells. And you can see on the right-hand side this mast cell, certain chemicals.

So the E antibody floats into your bloodstream, sits on mast cells. And then -- if we could have the next slide, Eric -- when you are reexposed to that pollen or that dust mite, these chemicals are released. Some are preformed. Histamine is probably the best known but there are others called leukotrienes and bradykinins. These chemicals get out. When these chemicals hit the cells in your nose, if they affix themselves to the glands, they cause extra mucus to be produced, giving you a runny nose. If they affix themselves to the nerves, they cause an irritation which gives us an itchy feeling and causes sneezing. And if they affix themselves to the blood vessels, they cause blood vessels to dilate and leak, so you get swelling around the blood vessels. We feel that as

congestion or blockage or a stuffy nose. So those are the symptoms that people experience and that is what we call the immediate reaction. So when, boom, you are exposed and, boom, you have a problem usually within the first hour. You will have symptoms.

But most people -- if we could have the next slide -- go on to have continued problems. And so in addition to those chemicals being released, there is something called cytokines, which you can see on the top left-hand side, and they call in from the blood vessels certain cells: white blood cells called the acidophils and basophils, and these blood cells get into the tissue and they release toxic proteins and they also release more of the histamines and more of the leukotrienes and you end up having more symptoms, ongoing symptoms, and what we call chronic inflammation. It's not just something that occurs within an hour like a light switch and then goes off again.

It continues, it's persistent. And in the airway, when it's inflamed, it stays irritable and it stays hyperresponsive. So it takes very little to keep it going. The allergin doesn't have to be very high. And you will keep on being symptomatic and you get an irritant response to things like paint and perfume and tobacco smoke. So your air is unstable and you become hyperresponsive. So that is the chronic inflammation that we see with allergic disease.

Q. **Now, is this the same or different from something like mucociliary clearance as a defense for the body?**

A. **Oh, it's different. The mucociliary is a process that has to do with anatomical structures. The little cilia that sit on top, as Dr. Kaliner pointed out yesterday, of our cells. The epithelium, the top lining of the nose membrane, has the little cilia that move our mucus along. This is immune system that has to do with antibodies that are made or cells that are parts of our system that get into that tissue that create the ongoing inflammation.**

MR. RICH: I think we have a slide, if we could, that talks about a lot of the symptoms that you talked about.

BY MR. RICH:

Q. **The primary systems, is that what you meant about the early phase reaction?**

A. **Early and late. We can see nasal symptoms both early and ongoing, people with nasal drainage, forward and backward, are called postnasal drainage. They can have this repetitive sneezing and spasms. Itchy nose, a wiggle called rabbit noses and they rub at it. The nose is blocked. They're stuffy. That is nasal symptomology.**

But many people, in addition to the nasal symptoms, have eye symptoms. They get itchy and watery, itching of their throat, itching of the pallet, itching of

the ears. And people, in addition to having the obvious respiratory symptoms, don't feel well.

Actually, we call allergic rhinitis a disease. And I like that word "disease" because if you break it in half, it's dis-ease. They just don't feel very well. And if they don't feel well. They complain of headaches more often. They don't sleep well. There is a recent survey that showed 40 percent of the people with nasal allergies don't sleep well, either have trouble falling asleep or staying asleep or waking up not as refreshed.

And if they don't sleep well, then clearly they don't perform very well at work, or at school for children. We actually have a term for that called presenteeism. People don't feel very well. They're there but they're compromised. So we're just not as good as we would be if we didn't have the disease, this allergic rhinitis.

Q. Do you differentiate between allergies based on the type of allergen?

A. There is a standard way of differentiating based on time of year or triggers. So what are the allergens that typically in places like Wilmington have these seasonality? Where I live in Southern California, it's much more blunted. We don't have snow, we don't have a lot of cold, so we have pollination really year around. So tree pollen goes in San Diego for five-six months. Here, it's for a few months.

Grass pollen -- and this is what we have at springtime. We'll have tree-and-grass pollination. And you will have, in the summertime, fallen weed like ragweed or others, sagebrush.

And then there are year-round allergens we call perennial allergens people are exposed to primarily inside the house. Dust mite is probably the most well known. Mold spores are a common trigger of this allergic mechanism and animal dander is extremely common. It's said that there is some 85 million cats now in the United States and 75 million dogs.

So there is a lot of people who are exposed. And if they have this susceptibility, then they will tend to be allergic year around. And many people have both seasonal and year-around problems because they're poly-sensitized. They're allergic not just to one thing. They're allergic usually to many, many allergens.

Q. **Is the symptomatology the same between seasonal allergic rhinitis and perennial allergic rhinitis?**

A. **Close enough. They end up having a little more problem, depending upon the allergin. Cat allergin tends to cause a lot of eye symptoms. Pollen allergin tends to cause a lot of eye symptoms. Dust mite, not so much, mold, not so much. There's a little variation, but similar enough that we don't really based on symptomatology. It's based on what**

the trigger is.

Q. I would like to turn your attention to corticosteroids, if I could. Why are corticosteroids used in the treatment of allergic rhinitis?

A. Corticosteroids are really our best anti-inflammation. Allergic rhinitis is an itis, and the term, the suffix itis really means inflammation, just like tonsillitis or appendicitis or arthritis are inflammatory problems, allergic rhinitis is an inflammation. If you can reduce that inflammation, that would be very helpful to the patients in terms of feeling better.

We know that the corticosteroids either systemically or topically can do a lot of what I pointed out in regard to that mechanism. So it can take mass cells and lower the numbers. It can take those cells that came in from the blood stream, the leukocytes, the base cells, and lower those numbers. We can reduce the cytokines and call them in. We can reduce the number of chemicals that are released. These have multi-faceted anti-inflammatory activity.

But they have to be taken routinely because if you stop pouring water on the fire and you still have the reason for the trigger causing the symptomatology, people again will become symptomatic. So you have to keep on keeping on with the medicine to keep the problem under

control.

Q. Are these steroid sprays taken topically or systemically?

A. The systemic clearly works, but it has too much baggage. So long ago, since the sixties and seventies, we tried to develop medicines which are anti-inflammatory that can only target the area where the problem is. And the intranasal corticosteroids have been a wonderful advance in terms of clinical care for the patients we see.

You can see them really divided into two groups, if you will. There is a group at the bottom, the three you see. The first two that came to be, actually, are not shown because I don't have a picture of them. They were Decadron Turbinaire, it was called, and the Beclomethasone Mini-Button. These were aerosol forms. And the aerosol has a little unit which is a cannister that is filled with the medicine. When you squeeze it, it sprays out. So an aerosol comes out in what we call a dry spray.

Subsequently, because those two medicines, and I will talk about that probably again, were problematic, additional aerosols were developed. But these that are shown are called chloro-fluoro-carbon delivery systems. That is to say, the propellant is called a chloro-fluoro-carbon or a CFC.

The world is agreed, as far as I know, on only

one thing, and that's to eliminate the CFCs because they affect the ozone layer. So there is now a Montreal Protocol. So by the end of this year, 2008, there will be no CFCs at all. So they are now developing new aerosol formulations, which will have a different propellant, called an HFA, a Hydrofil Alkane, which doesn't affect the ozone layer. We have these aerosol forms.

In addition, there were others that were developed that were a pump spray, a wet spray, if you will. You can see those listed on the top two rows, Declamethasone was one and flunisolide was another. Tricimdaline (phonetic) was another. We have a number. They keep being developed.

For example, the one in blue, Veramyst, just came out in 2007. The one Onerus (phonetic) just came out a month ago. So we are still developing new models that should be, in fact, can be helpful to people.

Q. You said beclomethasone. Is that the active ingredient in the Beconase AQ and the Vancenase?

A. Yes.

Q. And you said flunisolide is the next one. Is that the active ingredient in Nasalide and Nazorel?

A. That is correct.

Q. And then the active ingredient in Nasacort AQ is triamcinolone acetamine?

A. That is correct.
Q. What is the active ingredient in Flonase?
A. Fluticasone propionate.
Q. Nasonex, what is the active ingredient in that one?
A. Mometasone furoate.
Q. What is the mechanism of action that these steroids have?
A. Well, they act to reduce the inflammation, but interestingly enough, we look at them not only to reduce the inflammation but how they work in regard to symptoms.

So the rubber meets the road in terms of how well people get. And even if we have this large survey, it's not quite fast enough, so we have lots of options here. All of them are effective. All of them are effective in improving symptoms and all of them are effective in terms of reducing the impact on quality of life.

But even though they are all pharmaco-dynamically the same, that is to say, they all work, when you look at them pharmacologically, they are pharmacokinetics, that is to say how they are absorbed, how they are distributed, how they are metabolized, that is not quite the same.

Actually, Eric, I think we have a slide on that, which is interesting because, you know, they look at these molecules in preclinical work and try to figure out, is this

going to be effective.

You can see, for example, on the right side, you have mometasone and fluticasone propionate. And they would look to be better than triamcinolone on the left side in terms of binding affinity. That is to say when a corticosteroid is sprayed, it has to get into the cell, it has to bind with what is called the receptor.

And that complex is then transferred into the nucleus to make the activity that causes the anti-inflammatory process.

But it turns out these are not the same.

THE COURT: Yes.

MR. GRACEY: Your Honor, I have an objection about these not being the same. We are at the infringement part of the case. If he is going into areas that relate to obviousness or that sort of thing, I don't think that is appropriate. To give a general background I think is fine. Other issues I think is better for plaintiffs' rebuttal case.

MR. RICH: Your Honor, this is background. Second of all, it was in his opening expert report.

THE COURT: Overruled.

BY MR. RICH:

Q. Were you done with the answer?

A. No, no. It's surprising at some level for me, when

you look at these pharmacologically, and that's what I kind of hear about, preclinical information, before it gets to the clinic, that you would be able to distinguish. In fact, we have done studies, for example, on fluticasone and triamcinolone in a comparative study and shown no difference in terms of benefit. They work equally well. And they have the same microgram dose. For example, mometasone, the daily dose for Nasonex is 200 on the right. The fluticasone is 200 a day, and the triamcinolone on the left is 220 a day. So you would think if their affinity, that is how well they bind to the receptor, is so different, you would expect differences in terms of the clinical response and in terms of the dose needed to make it help. The same the thing happens if you look at this next slide. Not only is how well does it bind but how long will it stay bound. If it stays bound, theoretically, it should work longer and better. It doesn't seem to make a difference. For example, if you look at the middle one is, ciclesonide, when we studied that one recently, that was just released a month ago, the one on the far are right, Omnaris, that one is really not a very effective agent, even though it looks better than, for example, triamcinolone and it doesn't look much better than fluticasone in terms of safety.

You can't always tell from pharmacologic studies what you are going to see clinically.

Q. **Can you also differentiate between these products based on systemic adverse effects?**

A. **That is a very important differential. We look at efficacy in terms of do they benefit symptomatically. And then is there any side effect profile. First of all, we want to make sure we don't have systemic activity because the whole purpose of developing topical agents is so they don't affect any part other than where you are spraying it.**

We have looked at inhaled corticosteroids. We have looked at intranasal corticosteroids to see if much is absorbed and much stays in the system to affect other organ systems, like bone growth or eyes. And I know that there is a study we are going to be looking at of growth that's problematic, which was the Skoner article, that showed when we looked at beclomethasone, which was one of the older molecules, and studied that in children, the kids on that particular molecule didn't grow very well.

Q. **If I could ask you to turn to Plaintiffs' Trial Exhibit No. 375. Is this the Skoner article that you are talking about?**

A. **Right. This was a study that a number of us worked on, Dave Skoner from Pittsburgh, Gary Rajeleski (phonetic) from California, Paul Travinsky (phonetic) is from Massachusetts. We found some hundred children who we were able to study who had chronic nasal allergies. And half of**

them went on the beclomethasone nasal sprays, two spray per nostril, twice a day. And half of them went on a placebo spray, the vehicle basically of the aqueous formulation of beclomethasone. We found at the end of the study, at the end of the year, there was a growth slowing so that too much beclomethasone had gotten into the system, and because beclomethasone has a relatively high bioavailability compared to some of the newer compounds, it caused some growth change in children.

We also saw, interestingly enough, that the first one that I mentioned, we didn't have a picture of, Decadron Turbinaire, the reason that got pulled off the market so quickly is because when it was studied it caused suppression of the adrenal gland's normal output of cortisone. We make cortisone normally, and you don't want to mess with the body's normal production because it has all kinds of ramifications. And if it gets into the system, it will suppress your normal production which comes from your adrenal gland. And that initial product, dexamethasone, slowed production of normal adrenal production, and that is not a good thing, so that was withdrawn from the market.

Q. Getting back to this study that you worked on, the Skoner article, was that an aqueous beclomethasone dipropionate spray or aerosol?

A. That was the aqueous formulation of intranasal

beclomethasone dipropionate.

Q. **What products, what beclomethasone -- can I call it BDP?**

A. **Sure.**

Q. **What aqueous BDP?**

A. **That would have been Beconase AQ or Vancenase AQ.**

Q. **Has any study been reported showing the same growth suppressions results from the use of a CFC-propelled Beconase or Vancenase product?**

A. **No.**

Q. **You know, I just wanted to confirm, you are saying that there are these systemic effects, that is throughout the body, even though some products -- let me back up and ask it better. You are saying that some products have demonstrated systemic effects, effects throughout the body, even though they are applied only topically, only on the surface of a nasamucosa?**

A. **Yes.**

Q. **I would like, if I could, to turn to the subject of infringement, and if I could beg the Court's indulgence to put the boards up.**

Now I would like to turn to the issue of comparing Barr's ANDA product to the claims. If we could get the patent claims up.

Which patent claims were you asked to consider?

A. **I was asked to look at the patent, the '573 and the '329 for Nasacort. I was asked to look at the ANDA for Barr's product. I was asked to look at the package inserts for both Barr's product and the Nasacort product. And I was asked to look at the claim construction chart and the Court order of terms.**

Q. **So that was the universe of documents you considered in determining whether -- did you consider any other expert's testimony in relation to the infringement question?**

A. **I certainly considered the information that I learned from the experts who reported.**

Q. **And that would be Dr. Kaliner and Dr. Lockhead and Dr. Prud'homme and Dr. Berridge?**

A. **Yes.**

Q. **Now, where did you look to determine the attributes of Barr's ANDA product?**

A. **Well, I looked at the composition of the products. There were a list in the products that we could compare the two Barr products with the Nasacort product, the ingredients, if you will.**

Q. **I think we have a slide, a demonstrative comparing the Nasacort and the Barr product.**

You considered the package insert. Correct?

A. **This is the formula comparison I looked at. The ingredients are listed on the left-hand side and the**

function of those different ingredients on right-hand side. Basically, I was looking at the columns to see what was the percentage of the different ingredients in the Nasacort AQ compared to Barr's ANDA product. And they are nearly identical with the exception of benzalkonium chloride, which lists Nasacort as .015, and Barr's ANDA as .0155. Other than that, I could see really no difference or, they are nearly identical.

Q. The only difference you saw was five parts per million of weight in the benzalkonium chloride?

A. Yes.

Q. Turning to the package insert, was there anything that you learned there in terms of a summary of the product?

A. There was a product statement. This is the part that I noted particularly, because it had the same wording with the exception of, instead of it saying Nasacort AQ is, it says triamcinolone acetamine nasal spray is. Then it continues, is an unscented thixotropic water-based meter dose pump stray formulation unit containing a microcrystalline suspension of triamcinolone acetamine in an aqueous medium.

Q. Did you learn anything from the package insert with regard to the method of use instructed by Barr for the ANDA product?

A. They had a package insert, which we see here, again,

identical to the Nasacort AQ. So when you look at the two they look the same. It instructs people how to deliver the medication, which is in the unit, this pump spray that you hold with your thumb on the bottom and your index and middle finger on the top. You have put it in your nose. You aim laterally toward the back. You give a spray. You give a sniff. Then you do the other side. Then you go back and you do the first side and the second side.

So there is a standardization of how people are instructed, which is really very important to avoid side effects. So I appreciate those kinds of instructions. But they are identical.

Q. Now, did you form an opinion as to the infringement of Claim 6 of the '573 patent and Claim 26 of the '329 patent?

A. I did.

Q. And what is that opinion?

A. That Barr's product appears to infringe.

Q. Now, I want to go through element by element, except, thankfully, the parties have been able to agree that many elements are found in Barr's ANDA product. So I won't cover those with you. I know you originally considered certain admissions. But I would prefer if we could just to rely upon the uncontested facts.

Did you form an opinion as to whether Barr's

product is odorless?
A. I did.
Q. What is that opinion?
A. That it is odorless. The package insert says unscented. It's odorless.
Q. Is there anything that you drew from the list of ingredients that led you to that conclusion?
A. Well, it has phenyl ethyl alcohol in it. And phenyl ethyl alcohol --
Q. It has phenyl ethyl alcohol?
A. Excuse me. It does not have phenyl ethyl alcohol. I misspoke. And the absence of phenyl ethyl alcohol, which usually is the source of the odor or the scent, is not in either Nasacort or the Barr product.
MR. RICH: Your Honor, could I approach the diagram?
THE COURT: Yes.
BY MR. RICH:
Q. So could we put a check in the odorless box?
A. Yes. There is one other reason. I had the opportunity -- Dr. Prud'homme talked about what he did yesterday. One of the things I did yesterday was spray it in my nose. And as a pediatrician, you get used to tasting things that kids are going to have to taste. And if somebody cares about what people have to experience, I often

spray the sprays to feel what they feel like. So I had, last night, an opportunity to spray Barr's product. And I didn't sense any odor at all.

Q. With regard to the element of imparting to the composition the following thixotropic properties, do you have an opinion on that portion of the claim?

A. I do but I rely on Dr. Prud'homme for that.

Q. So can we put a check in there based on Dr. Prud'homme?

A. Sure.

Q. And the viscosity of the composition in unsheared form is about 400 to about 800 centipoise?

A. My opinion is consistent, but I rely on Dr. Lochhead for that.

Q. And that the composition is subjected to shear or shaken in preparation for spraying, the viscosity of the composition is about 50 to about 200 centipoise?

A. Again, I rely on Dr. Lochhead for that, but I would affirm that.

Q. The limitation is for deposit on the mucosal surfaces of the nasal cavity. I guess it's the material deposits on the mucosal surfaces of the nasal cavity.

A. Again, I would rely on Dr. Berridge for that.

Q. And that in deposited form on the mucosal surfaces, the viscosity of the composition is about 400 to about 800

centipoise.

A. **Again, I affirm that, but I rely on Dr. Prud'homme.**

Q. **Such that it resists being cleared from the mucosal surfaces by the inherent mucociliary forces which are present in the nasal cavity. Do you have an opinion on that element?**

A. **I do, and I rely on Dr. Berridge's testimony.**

Q. **So your opinion is that all the elements of Claim 6 of the '573 patent are found in Barr's ANDA product?**

A. **Yes.**

Q. **Turning to Claim 26 of the '327 patent. Can you see that?**

A. **No, not a chance. I have a cheat sheet over here.**

Q. **Do you believe that Barr's ANDA product is thixotropic as required by that claim?**

A. **I do. I rely on Dr. Prud'homme for that claim.**

Q. **Do you have an opinion as to whether the use of Barr's ANDA product is a method for delivering the aqueous thixotropic pharmaceutical composition to each of the mucosal surfaces of the anterior regions of the nose, the frontal sinus and the maxillary sinuses and on each of the mucosal surfaces which overlie the turbinates covering the conches?**

A. **I rely on Dr. Berridge for that.**

Q. **Do you have an opinion as to whether the method**

allows the sprayed composition to deposit on the surfaces?

A. **I rely on Dr. Berridge for that.**

Q. **Do you have an opinion as to whether the method causes it to deposit in the form of a viscous composition?**

A. **I rely on Dr. Prud'homme on that.**

Q. **Do you have an opinion as to whether the viscous composition in the method resists being cleared from the mucosal surfaces by the inherent mucociliary forces which are present in the nasal cavity?**

A. **Dr. Berridge comments.**

Q. **And do you have an opinion as to whether the suspending agent used in the method imparts to the composition the following thixotropic properties: that the viscosity of the composition in unsheared form is about 400 to about 800 centipoise?**

A. **Dr. Lochhead's comments.**

Q. **And as the composition is subjected to shear or shaken in preparation for spraying, the viscosity of the composition is about 50 to about 200 centipoise?**

A. **Again, Dr. Lochhead.**

Q. **And so do you have an opinion as to whether the suspending agent imparts to the composition those thixotropic properties?**

A. **I do. As per my comments, both Dr. Lochhead and Dr. Prud'homme have commented on those.**

Q. So your conclusion with regard to Claim 26 as well is that Barr's ANDA product infringes that claim?
A. Yes.
MR. RICH: Thank you. I have no further questions, Your Honor.
THE COURT: All right. Counsel, you may cross-examine.

CROSS-EXAMINATION

BY MR. GRACEY:
Q. Good afternoon, Dr. Meltzer.
A. Good afternoon, Mr. Gracey.
Q. We haven't officially met yet or even unofficially, so I'm Taras Gracey. It is nice to make your acquaintance. I did not have the honor of taking your deposition. That was my colleague, Ms. Johnson. But I just wanted to ask you a few questions about your background, and then we're going to talk a little bit about some of your opinions here.
You testified that you are here on behalf of Aventis as an expert witness. Right?
A. Check, yes.
Q. Check. And you're being compensated for your time?
A. Yes.
Q. Approximately $400-450, whatever it is.
A. Yes.
Q. And I think you also testified that you had done some

work for Aventis before amongst many other pharmaceutical companies?

A. Yes.

Q. But you have also done a little more than that for Aventis. Right? You actually have been an expert witness for Aventis?

A. Yes.

Q. And I that is I think in the Allegra case?

A. Yes.

Q. That case is still ongoing, I believe?

A. Yes.

Q. And actually that case is against Barr, isn't it? Or do you know? Maybe you don't know. It doesn't matter.

Now, you have also received research support in the past from Aventis. Right?

A. Yes.

Q. Okay. Now, you have testified about your background and your education and what not. But I just wanted to clarify a few things. You have given some opinions here based on relying on others but I just want to clarify you are not an expert in formulation. Right?

A. Yes, that's correct.

Q. Okay. And that would also mean you are not an expert in designing pharmaceutical formulations. Right?

A. That is correct.

Q. **And that would also include nasal formulations. Right?**

A. **That is correct.**

Q. **Okay. And indeed, you have never designed any thixotropic compositions?**

A. **I have not.**

Q. **Okay. You are not an expert in rheology?**

A. **I am not.**

Q. **All right. And are you not an expert in positron emission tomography or PET?**

A. **I am not, but I can say it.**

Q. **Okay. I can't.**

You are not a board certified surgeon. Right?

A. **Correct.**

Q. **And as such, you are the also not an ENT surgeon?**

A. **I am not.**

Q. **We do have an ENT surgeon here. I believe you know Dr. MacKay?**

A. **And respect.**

Q. **Thank you. We'll be hearing from him in a little bit. You are also not an expert in viscosity?**

A. **Correct.**

Q. **Indeed, you didn't do any viscosity testing on Barr's product. Right?**

A. **I did not.**

Q. **I just want to put this first board back up.**

MR. GRACEY: I'm sorry, Your Honor. May I put the board up?

THE COURT: Yes.

MR. GRACEY: Thank you. I'm sorry.

BY MR. GRACEY:

Q. **Okay. Now, I believe you testified that you don't have any independent opinion on infringement, on the viscosity claims at issue in this case, do you?**

A. **Correct.**

Q. **Okay. And, in fact, I think you said you're completely relying on Dr. Lochhead regarding Barr's viscosity?**

A. **Correct.**

Q. **All right. And then you didn't personally do any analysis to determine if Barr's product is thixotropic as defined in the patent. Right?**

A. **Correct.**

Q. **Indeed, you don't have any independent opinion on infringement for the thixotropic claims at issue in this case. Right?**

A. **I do not.**

Q. **All right. I think you said you are relying on Dr. Prud'homme for those conclusions. Correct?**

A. **That is correct.**

Q. **All right. Now, you don't know where specifically Barr's product is delivered, do you?**

A. **No, my limited experience is one, and end of one, namely me.**

Q. **You don't know whether therefore Barr's product infringes on the frontal sinus. Is that right?**

A. **I do not.**

Q. **All right. You didn't do any PET studies of Barr's product to determine whether it deposits on the frontal sinus. Right?**

A. **Correct.**

Q. **In fact, Dr. Berridge didn't do any PET studies on Barr's product to determine whether it deposits on the frontal sinus, did he?**

A. **I believe that's the way he testified.**

Q. **Just so the record is clear, you believe he -- let me just ask you. I want to make sure the record is clear. Dr. Berridge did not do any testing on Barr's product to determine if it entered the frontal sinus. Isn't that right?**

A. **I think that is what he testified to.**

Q. **Thank you. So it's fair to say that you don't have any independent opinion about whether, in fact, Barr's product enters the frontal sinus, do you?**

A. **I do not.**

Q. **All right. You are in fact, as we stated, completely relying on Dr. Berridge's PET studies related to Nasacort AQ. Right?**

A. **Yes.**

Q. **All right. Indeed, prior to your deposition, you have never even spoke to Dr. Berridge, did you?**

A. **That is correct. Prior to meeting him here, I have never had a personal conversation with him.**

Q. **Perfect.**

MR. GRACEY: Thank you, judge. That's all the questions I have.

THE COURT: All right. Is there anything else?

MR. RICH: Hopefully, I only have one question.

THE COURT: Okay.

REDIRECT EXAMINATION

BY MR. RICH:

Q. **Before forming your opinion as to infringement, did you view Dr. Berridge's expert report?**

A. **I did.**

MR. RICH: Thank you, Your Honor.

THE COURT: Doctor, thank you. You may step down.

MR. BERGHOFF: Your Honor, with the only exception being the housekeeping details of submitting our deposition designations to Your Honor, plaintiffs will close

their case-in-chief.

THE COURT: All right. Are you ready for Barr's case?

MR. HURST: Your Honor?

THE COURT: You need some time to set up?

MR. HURST: No, we do not. Actually, I was wondering, I would like to make a motion for judgment as a matter of law under Rule 52(c).

THE COURT: Go ahead.

MR. HURST: Yes?

THE COURT: Yes.

MR. HURST: I had two points to make, two claim elements to focus on.

The first is deposition in the frontal sinus. It's required by both asserted claims, and the only evidence you have heard from Aventis was Dr. Berridge's PET scan. First, Dr. Berridge's PET scanning was not in the Barr's product. It was with Nasacort. Nobody did any PET scanning with Barr's product to determine whether it reached the frontal sinus. The only testing that was done was with Nasacort.

THE COURT: Is there a departure with regard to? There has been testimony the products are identical.

MR. HURST: Except with respect for viscosity. The testimony you have with respect to shear viscosity,

which is what matters in terms of getting to the frontal sinus, is Dr. Lochhead's testimony. Dr. Lochhead put Nasacort side by side with Barr's product and he saw that the shear viscosity of Nasacort was from 60 to 68. He tested Barr's product and the shear viscosity was 100 or more, so you are talking 60 percent increase.

There has been no testing at all in this case by anybody, a complete absence of evidence over whether that difference can impact whether or not a product gets to the frontal sinus. And, if anything, there is evidence to show that it does not. If you remember, Dr. Berridge said when the product cooled, which actually increases viscosity, in his 2002 test, he got zero frontal sinus deposition. Well, Barr's product has a higher viscosity than Nasacort.

So the point being you really have to test Barr's product which is manufactured at a different plant under different conditions. Who cares if -- and if the formulation is the same, as Dr. Lochhead acknowledged, you get different viscosities from different manufacturing procedures.

So that is of the first point, Your Honor. No testing of Barr's product which has a different viscosity according to the undisputed evidence in the record.

The second point is this: If you were to accept everything that Aventis says, every single thing, all

they're saying and arguing is that our testing shows that the product reaches the frontal sinus in 6 of 14 patients, a little less than half the time. That is the argument Aventis has made with their evidence. If you accept every word of it, if I accept it, they still lose as a matter of law and here is why.

There are only three ways to prove infringement:

One is direct infringement. No evidence that Barr is actually administering a drug to anybody in the frontal sinus so they have to rely on contributory or inducement.

With respect to contributory infringement, there is no infringement as a matter of law as long as a product has a substantially non-infringing use, which Aventis has proven. They have proven up that the product, according to them, if I accept all their evidence, it gets to the frontal sinus less than half the time; which means there is a noninfringing use: the use of the product in those 50 percent or more occasions when it doesn't get to the frontal sinus. So no direct infringement, no contributory infringement as a matter of law. And,

Finally, certainly no inducement to infringe, which, as you know, is an intent-based infringement. They have to show intent that Barr is inducing people to use the product to reach the frontal sinus. And, obviously, we

don't believe it happens. There has been no evidence that we have an intent to induce people to use our product to reach the frontal sinus.

So that's frontal sinus issue. Next we're going to talk about the viscosity of our product in the nose. That is one of the elements of the claim. That after deposit, the product increases, thickens up to 400-to-800 centipoise. 400-to-800 centipoise.

You heard no evidence that there was any testing done on Barr's product under the conditions of the nasal cavity. It just was not done. The most you have heard from Dr. Prud'homme today is he believes there would be a thickening. That is what he said. But what you didn't hear is any evidence at all that that thickening would reach the required 400-to-800 centipoise. Again, a complete absence of evidence. And the reality is even his testimony for the thickening, he was relying on reports from FMC and Hydan which was work with Nasacort, not with Barr's product.

So for those reasons, Your Honor, we make a motion for judgment as a matter of law under Rule 52(c).

THE COURT: All right.

MR. BERGHOFF: We think the evidence at this stage, viewed by the very high standard that would be on Barr at this point in mid-trial, clearly supports that we are entitled to go forward on our burden of a mere

preponderance of the evidence to show infringement of each element.

In terms of deposition on the frontal sinus, Dr. Berridge's testimony is clear. In the two studies that he did, where he obtained reliable data, six of eight patients saw measurable, noticeable deposition of Nasacort AQ in the frontal sinus, and deposition that lasted well over an hour. It was not an artifact. It was real data.

And the 2002 study, which Barr's counsel argumentatively would like to be discounted, which is inappropriate at this stage, is based on unreliable data. That is, Dr. Berridge's testimony, that that data was unreliable. Therefore, he didn't publish it. In fact, he pointedly told Aventis that the data showed unusual variations and could not be relied on. So that data should be eliminated from the consideration.

So the evidence of record shows that Nasacort AQ, which is identical in formulation to Barr's ANDA product, there has been no dispute on that, deposits in the frontal sinus in six of eight patients. So there is no issue here on whether it happens or not. It does. And the use, the intended use of Barr's ANDA product, should it be released to the market, will result in deposition of their product on the frontal sinuses of a substantial number, we believe most, the strong majority of patients who use the

products, and our evidence supports that.

So we think their motion is ill-taken on that.

In terms of the viscosity in the nose, Dr. Prud'homme was very clear that it was his opinion that the evidence before him leads him to the conclusion, because of his expertise, that Nasacort AQ or Barr's ANDA product, take your pick, they are identical, will result in the original setting viscosity of 400 to 800 after it is deposited in the nose.

And he dealt with the counter-arguments from Barr's counsel that they would like you to just adopt at this point, about the cilia and the temperature and the dilution effects in the nose. He dealt with those and said, in his opinion, they would not change the result. The result is that Barr's ANDA product will go from its original setting viscosity down, when it's shaken and sprayed, and very quickly recover to its original setting viscosity within the 400 to 800 range.

And we believe the evidence clearly supports our position, exceeds by a good margin the preponderance of the evidence.

So we would ask Your Honor to deny Barr's motion.

THE COURT: The Court agrees with Aventis that it is premature at best at this point, would be, for the

Court to rule in Barr's favor. I will deny the motion. Let's move on.

MR. HURST: Thank you, Your Honor. Our first witness will be Dr. MacKay and Mr. Taras Gracey will handle that witness.

... IAN S. MacKAY, having been doing sworn as a witness, was examined and testified as follows ...

DIRECT EXAMINATION

BY MR. GRACEY:

Q. **Please state your full name?**

A. **Ian Stuart MacKay.**

Q. **I won't be using a binder with Dr. MacKay today. Please state your home address?**

A. **Home address is 8 Compound Mansion, Part 4, London.**

Q. **Are you currently employed, Dr. MacKay?**

A. **I am self-employed in private practice in harvestry.**

Q. **What kind of doctor are you?**

A. **I am an otolaryngologist, which is an ear, nose and throat surgeon, also known as an ENT surgeon.**

Q. **Let me ask you, where do you have privileges today?**

A. **I have admitting privileges to King Edward VII Hospital in London.**

Q. **Is that a hospital that treats the Royal Family?**

A. **It does.**

Q. **And have you yourself treated the royal family?**

A. **I have.**
Q. **Let's talk a little bit about your educational background. Could you, starting with high school, tell the Court a little bit about your background?**
A. **My undergraduate training was at the Royal Free Hospital in London, which is part of London University. And then after qualifying in 1968, which is exactly 40 years ago, I did two years of house jobs and senior house officer jobs, before training to be an ear, nose and throat surgeon at the Royal National Throat and Ear Hospital in London.**
Q. **You used the term house jobs. I think of that in terms of sweeping a floor. Can you explain what that means?**
A. **They are junior posts in the hospital hierarchy.**
Q. **But they are medical posts?**
A. **Yes.**
Q. **Now, did you obtain your -- did you become a Fellow?**
A. **I became a Fellow of the Royal College of Surgeons of England in 1974.**
Q. **And then when did you complete your certificate?**
A. **I completed my certificate of specialist training in 1976.**
Q. **Now, have you or do you do any teaching?**
A. **I do. I teach on two courses. One is the rhinoplastic course and the other is the rhinosinusitis course.**

Q. **Rhinoplastic, what does that mean?**

A. **That's changing the shape of the nose. Shape and function.**

Q. **And the second?**

A. **Is to do with rhinitis, rhinosinusitis, sinus surgery.**

Q. **Rhino, does that refer to anything in particular?**

A. **Rhino, noses, as in rhinoceros.**

Q. **Approximately how many students have you taught over your career?**

A. **Well, post-graduate would be probably two and a half to three thousand, something like that. I also used to teach undergraduate students at Charing Cross Hospital, which is an undergraduate teaching hospital, part of University of the London.**

Q. **Have you been a visiting professor anywhere?**

A. **Yes, I was a visiting professor at the Mayo Clinic at Rochester about 12 years ago, in 1996.**

Q. **Here in the U.S.?**

A. **Here in the U.S.**

Q. **Now, let's talk a little bit about the Royal Brompton Hospital. What did you do there?**

A. **I set up -- the Royal Brompton is the National Heart and Chest Hospital. And respiratory diseases and sinus diseases are very similar, which is not surprising, because**

the lining of the nose and sinuses and the lining of the lung is the same sort of tissue.

I realized, having been appointed there, quite quickly, that this was quite a unique experience, to see patients with some very interesting nasal and respiratory conditions, and set up what was actually a multi-disciplinary clinic, looking at nasal problems.

Q. You said you established a nose clinic there?

A. That was the nose clinic, yes.

Q. When did you establish that?

A. That was about 1979, probably.

Q. So how many years -- did you run that clinic?

A. Twenty-seven years.

Q. Now, let's talk about your work at Charing Cross Hospital. What was your position there?

A. Well, eventually I was the head of the department at Charing Cross.

Q. Which department?

A. The ear, nose and throat surgery.

Q. Are you a member of any professional societies?

A. I am a member of the British Association of otorhinolaryngologists, head and neck surgeons, which is the equivalent of the American Academy of Otolaryngology.

Q. Did you hold any posts there?

A. I was the president for three years, starting in

1999.

Q. **Approximately how many members does that association have?**

A. **A little over a thousand. About 1100 members.**

Q. **Approximately how long have you been practicing medicine?**

A. **Forty years.**

Q. **Have you ever -- you stated you are a surgeon. Right?**

A. **I am a surgeon.**

Q. **Have you ever operated on the nose?**

A. **I have, strangely.**

Q. **How many times, approximately, over your career?**

A. **Yes. As others have found, it's quite difficult to put a number on this. Actually, I do have a pretty good idea, because unlike just seeing patients, we do audit our surgery and have done for many years. And for many, many years, I was doing approximately 400 operations per year, it's not quite as much as that now, because I have slowed down, but it would come to certainly in excess of 10,000 operations on the nose.**

Q. **Now, have you ever operated on the frontal sinus?**

A. **Indeed.**

Q. **And approximately how many times have you operated on the frontal sinus?**

A. **In the region of a thousand times.**
Q. **Now, do you see patients with any nasal problems?**
A. **Yes. I am a rhinologist. I virtually see only patients with nasal problems.**
Q. **How many of the patients that you have seen over your career have what's been termed allergic rhinitis?**
A. **We audited that, when I was at the Brompton. And approximately -- it was just under 25 percent of the patients had allergic rhinitis. Just over 25 percent had non-allergic rhinitis. And then the remainder were either rhinosinusitis, which is infection in the sinuses, or nasal polyps, or some other nasal problem, structural problem.**
Q. **Do you only treat your patients with surgery?**
A. **I operate on only about one in ten of the patients I see. So the vast majority of patients with rhinitis are treated with medical treatment, not surgical treatment.**
Q. **Does the medical treatment include corticosteroids, such as Nasacort AQ and Barr's ANDA product that is at issue in this case?**
A. **Intranasal steroids are the main treatment, yes.**
Q. **Approximately how many patients do you believe you have treated with intranasal steroids?**
A. **Very difficult to tell. I would say I treat, there are 50 to 75 percent of the patients I see with intranasal steroids, so vast numbers.**

Q. **Now, based on your experience and the surgeries, do you feel that you know the nasal anatomy?**

A. **I do feel I know the nasal anatomy. It's very important, if you are operating on somebody's frontal sinus, you need to know the anatomy.**

Q. **In fact, do you consider yourself an expert in the nasal anatomy?**

A. **I do.**

MR. GRACEY: Your Honor, at this time I would offer Dr. Mackay as an expert in the treatment of rhinitis, treatment, as well as the nasal anatomy.

MR. RICH: No objection.

THE COURT: He is accepted.

MR. GRACEY: Thank you.

BY MR. GRACEY:

Q. **Dr. MacKay, did we ask you to offer an opinion in this case?**

A. **You did.**

Q. **What was the opinion we asked you to offer?**

A. **You asked me to offer an opinion on deposition of nasal sprays in the frontal sinus.**

Q. **Briefly, what is your opinion?**

A. **I think it is extremely unlikely, if not impossible.**

Q. **Again, briefly, why not?**

A. **Very briefly, because the pathway from the nose to**

the frontal sinus is a very narrow, tortuous route, which goes backwards, and downwards. And I think it's very unlikely that a spray would be able to get up there.

Q. Now, again, you have sat in the courtroom. You have heard what a large part of this case is about. It's whether Barr's ANDA product would, in fact, reach the frontal sinus. Let's talk a little bit more specifically about the frontal sinus. Did you and I put some demonstratives together to help us?

A. We have.

Q. Do you have your pointer?

A. We do.

Q. If we can see the first demonstrative, please.

Please explain for the Court what we are seeing here?

A. Well, this is a very similar drawing to the drawing we saw yesterday of Dr. Kaliner. And so this is a lateral view, side-view of the nose. Here is the frontal sinus. This is the brain. This is the sphenoid sinus. We have got the hard pallet. And here is the vestibule of the nose with the head, this would be the inferior turbinate, the middle turbinate, the superior turbinate.

Q. Let me stop you a second so we understand. What part of the face are we seeing?

A. Well, we have sliced the head down the middle, that

way (indicating).

Q. You are seeing this part --

A. We have removed the left part of the head and we are looking at the right part. But we are just at the part of the septum that divides the left and the right. So we are just beyond the septum. Otherwise, we would just be looking at the septum.

Q. Let's talk a little bit about how a nasal spray, the path that it would take in order -- first, let's talk about a nasal spray and generally the places where it would start to hit?

A. Well, it would first have to go past the nasal valve. But that's usually achieved by putting the nozzle of the spray just inside the nose beyond there.

It would then spray onto what I would call the atrium, this area here. You remember, this area, incidentally, is covered with skin. So that's squamous epithelium. That's the vestibule.

Q. So squamous epithelium is just another name for --

A. Pavement cells. But skin, like everywhere else.

The turbinates are covered with ciliated mucus membranes -- sorry, ciliated columnar cells, which we heard about yesterday. In fact, this area is slightly different, this is actually transitional epithelium and it doesn't have the hairs that the rest of the nose does.

Q. **You used the word epithelium. Again, could you just explain what that term means?**

A. **Designing of the nose, yes, mucus membrane, which is relevant, because a spray going into this area will very likely deposit it in this part of the nose which is sometimes called, in some of these studies it's been called the anterior part of the nose or the front part of the nose, and that's quite relevant because there probably isn't any clearance from that area.**

Q. **In fact, one of the things be Aventis has claimed in marketing documents and other things is that it stays where it's sprayed when we are talking about Nasacort AQ. Correct?**

A. **Indeed, absolutely.**

THE COURT: Doctor, when you say that area, what you were circling, where there is likely no clearance, what is that area?

THE WITNESS: Well, that's the atrium of the nose or the anterior part of the nose. And it's quite probable that spray going into that area will just sit there.

BY MR. GRACEY:

Q. **Do we have another demonstrative that will further explain --**

A. **Just before we go to that, if we are talking about a**

spray going up into the frontal sinus, the first thing it would have to do is make its way without touching anything, because don't forget, this will stick to whatever it impacts with.

Q. Stays where it's sprayed?

A. So it is going to have to go in between the middle turbinate and the lateral wall of the nose.

Q. So it looks from here like the entrance to the frontal sinus is right there. Is that not it?

A. Well, no, it's a lot more complicated than that.

Q. But above that?

A. No, there is nothing there, no.

This is the middle turbinate. And if we go to the next picture, this, we have removed the middle turbinate and the interior turbine. But this is a drawing. And this is the drawing that Dr. Kaliner showed yesterday.

That looks like the opening to the maxillary sinuses. The maxillary sinuses you may remember are these cheek sinuses here. So these opening -- that's actually an accessory ostium, a little extra opening, because the natural ostium is just a little bit in front of that.

But this is called the bulla, the bulla ethmoidalis. That is another swelling, and that, if you like, is full of, like a honey come of cells.

So between the eyes, here, one has the ethmoid

sinuses, you have got the frontal sinuses, the maxillary sinuses and the ethmoids. The ethmoids are very much like a honeycomb of air cells, again, lined with ciliated mucus membrane.

And in addition to that there is a sphenoid.

To get up into the frontal, yesterday, we learnt that the opening is here. And it's true that perhaps that's the opening to the beginning of what is actually quite a long pathway up into the frontal sinus. It isn't just a round opening that opens straight into the frontal sinus. We still have got a long way to go.

If I may --

Q. Just so the record is clear, we are looking at a diagram?

A. Yes. Absolutely. This is a diagram. So what I would like to do is to look at the real thing.

Q. Next slide, please.

A. This view, when we get it, is going to be a head. Needless to say, the patient is dead. This is the right eye. This is the left eye.

This is the brain. This is the septum. This would be the tongue. You can see teeth here.

These are the turbinates. Now, normally, the turbinates would be much more swollen than that. They would be engorged with blood. And, in fact, they swell up and

shrink down all the time, depending on the air that we are breathing and whether you drink alcohol and whether you have allergic rhinitis and all those sort of things.

But here they are very shrunken. So normally they would be much more swollen. So these are the sausage-shaped things going from the front to the back. So the inferior turbinate and the middle turbinate. You can't see the superficial turbinate in this.

You can see this already, because it is going to have to come to this area. There is not much flow in this area, because it will bump into that bulla.

Q. When you say it, what are you talking about?

A. Flow of air. So it is going to have to go between the middle turbinates and the lateral wall of the nose.

Q. If I may, let's go back one side, if we can. We are also talking about whether a nasal spray would get to the frontal sinus?

A. Absolutely.

Q. It is the same direction that a nasal spray would have to go?

A. Absolutely right.

Q. So we are clear, in this picture, the front of the face has literally been cut off?

A. Absolutely.

If we go now to the next picture, this is the

actual thing, if you like. We talked before about the diagram. This is the actual anatomy. So here is the nostril, with the hairs. That would be the nasal valve. This is the atrium of the nose, the anterior part, which is smooth. Here is the frontal sinus, up here.

Having gone -- don't forget, the middle turbinate has been removed, so we can see far more easily into this area than you normally would do. But assuming that you have been able to get the spray to go between the middle turbinate and the lateral wall of the nose, it is going to have to turn around here and come back up. This is the area that it's going to have to make its way out, through this extremely narrow pathway here.

And this is, if you like, the frontal nasal duct although a lot of people don't like the term duct because it is not really a duct. It is sort of a pathway. It is not a true duct.

From that area, which Dr. Kaliner was talking about yesterday, it's got about one and a half centimeters to go in order to get from that area up to the frontal sinus.

It's got to go up. Not only will it stick to things on the way, and not only did it have to get between the middle turbinate and the laterally wall, but it's also got to make its way up this very, very narrow pathway,

again, without sticking to anything, against gravity, and also against the ciliary activity.

You saw that beautiful demonstration yesterday of the ciliary flow. That's actually going to be going in the opposite direction, because the flow is downwards, and backwards.

So this spray is going to come in, do a turnaround, go up this very narrow airway.

Another thing that actually Dr. Kaliner said yesterday, which I thought was interesting, was he was talking about when we come down in an airplane and how many of us have experienced frontal pain, from the airplane descending. Actually, the reason we get the frontal pain is because the air can't get back out. Normally, the pressure, when we are flying up high, is, the pressure outside is low so the pressure inside is low.

As you come down the pressure builds up on the outside. So you have a relative vacuum which is why you have to blow to get the air back into your ears. It is the same, you need to get the air back into your frontal sinus. And the slightest bit of obstruction, whether due to allergy, infection, or cold, or even if you had some alcohol, which causes vasodilatation, it gets blocked. That's why you get the headache when you're coming down. It's because it's so narrow, so tortuous. And the slightest

bit of swelling blocks it off.

Q. Dr. MacKay, right here, is this a person who is suffering from inflammation?

A. Well, he is certainly suffering from something.

Q. Because they are dead. Right?

A. Yes.

Q. Would this pathway be less or more narrow than the person suffering from inflammation?

A. In a cadaver, in a dead body, the tissue is relatively shrunken up. So it would be more swollen than that. And it's vascular because it swells up and shrinks down.

Q. Now, Dr. MacKay, the flow of the -- you have also heard this area here is called the frontal sinus drainage pathway. Correct?

A. Absolutely.

Q. And gravitationally, which way is that flowing?

A. Downwards and backwards.

Q. All right. Okay. Now, Nasacort AQ, the drug that is at issue here, is a corticosteroid, I believe you testified?

A. It is.

Q. Let's take a look at the next slide. Explain to the Court what we are looking at here?

A. Well, this is going back to the same side view that we are getting used to seeing. And this is a mixture of a

drawing and a CT scan. A CT is computerized tomography, but it is basically an x-ray. This is again the real thing inasmuch as here's is the sphenoid sinus, that one at the back. This is if frontal sinus, this is what's called the front ethmoidal recess. And here you can see the pathway. It nicely shows the honeycomb of cells, the ethmoid cells, that surround this pathway.

Q. I think we heard Dr. Kaliner testify yesterday that he believed, I think, that all of this is the frontal sinus. Do you recall hearing that testimony or something similar?

A. I think the impression was that the opening to the frontal sinus was fairly low down and that it went straight into the frontal. I think that's all.

Q. And if you could explain to the Court, just sort of point out again, where does the frontal -- where is the frontal sinus?

A. That is the end of the frontal sinus there because that's the ostium, from there on, it's not actually the frontal sinus.

Q. Now, plaintiffs have claimed that a nasal spray, that Nasacort AQ, sprayed into the nose, would make it into the frontal sinus. You are aware of that. Right?

A. I am.

Q. Do you agree with that opinion?

A. I think it is -- one is terribly tempted to say it is

impossible. But I know it is not a very good thing to say anything is impossible. But it is nigh on impossible. It is extremely unlikely, to the point where I think it's virtually impossible.

MR. GRACEY: And let's show another slide, another slide, which, actually, if you can get to the next slide.

BY MR. GRACEY:

Q. **And explain what the arrows here are indicating.**

A. **Well, these are the pathways, the drainage pathways which drain the mucus down and backwards into the throat. And the whole time, these are draining in the opposite direction to the way you would want to -- the way they would have to go if you are going to get a spray to go back upwards.**

Q. **So this would be something that would be assisting or making it more difficult?**

A. **Making it more difficult.**

MR. GRACEY: Now, let's see the next slide.

BY MR. GRACEY:

Q. **Explain for the Court what we're seeing here.**

A. **Well, this is what happens, what would have to happen for a spray to get into the frontal sinus.**

MR. GRACEY: And if you could go to the next slide.

BY MR. GRACEY:

Q. All right. Now, what does the green indicate and then the red?

A. Well, the green indicates where it is going and it would normally continue to go around here and downwards. But for it to have to turn around and go against gravity and back on itself and not touch anything either, because if it touches anything on the way it's going to stick and stay there, I just think it's completely impossible.

Q. All right. Doctor, now how is it that you are so familiar with the frontal sinus?

A. Because I operate on it.

Q. And what are the methods of operating on it?

A. More than that, I actually examine the nose. I see even now as a semi-retired man, working part-time, I see about 1,500 patients a year. I'm a clinician, I'm not a scientist. And I'm at the shop end, literally. But every single patient I see, I examine their nose with an endoscope. And I can tell you that you cannot see up into the frontal sinus; certainly not unless you do an awful lot of maneuvers and take a very angled telescope; and even then, you are never absolutely certain.

Q. And is there only one way to operate on the frontal sinus?

A. No. For the first 10 years of my career, I operated

on the frontal sinus via what we call an external approach. And in some ways, that is quite a safe approach. But you make an incision so you are in this area, and you drill a hole into the sinus, and then you might open up the ethmoids.

Q. Dr. MacKay, before you go on, just for the record, can you just describe what you were doing?

A. Absolutely. You make an incision just underneath the eyebrow, on to the nose, the nasal bridge as it were, and then drill a hole through the bone upwards into that frontal sinus.

Q. All right. So you have actually seen the frontal sinus with your own eyes?

A. I have.

Q. And is there another way to operate?

A. Yes. Nowadays, the last 20 years, we've done this, when we can, endoscopically. You still have to be prepared to do it externally because very often, despite everything we have done, when we operate on this, there is no way of getting up here other than by removing all these ethmoidal cells to get there. There is no other way of doing it. You can't just go up here. So we look up with an endoscope. You take special forceps, and you remove all these little partitions of bone in order to try and get your way up into there.

Q. **Is it a danger-free operation?**

A. **No, it certainly isn't. It's potentially extremely dangerous because you can kill a patient. You can give them cerebrospinal fluid leak. That's fluid that bathes around the brain. You can give them meningitis. You can make them blind.**

This is why, if it was possible to treat the frontal sinus with a spray, I'd be very happy.

THE COURT: Those dangers you described, do they result during surgery from the instruments that are used?

THE WITNESS: They do. It's worth just adding, though, that you could also have those sort of the complications. I'm putting it rather dramatically, but it does happen from surgery. The incidents of serious complications from sinus surgery is about 1 in 1,000.

THE COURT: So the cribriform layer is where?

THE WITNESS: The cribriform plate is actually -- if I said here, it's not quite right, because this is not quite where it is, but it's in that area.

BY MR. RICH:

Q. **And what is that?**

A. **The cribriform plate is where the olfactory, the nerves that you smell with that come down from the brain into the olfactory part of the nose, which is the part that you smell with, which right up at the top, near the superior**

turbinate.

Q. And so if you had your choice about whether to operate on the frontal sinus or use a nasal spray, if you knew it was going to get into the frontal sinus, which would you have chosen?

A. I always try to treat these patients medically in some way if I possibly can. And, of course, a lot of them one can treat with topical steroids. I'm not suggesting everybody with frontal rhinosinusitis or chronic frontal sinusitis would be treated this way or indeed surgically. But when medication fails, then we have no option.

Q. And again, you are not saying that you use the medication to treat the frontal sinusitis. Right?

A. I do use internasal steroids, but I use drops because I don't believe the sprays would get anywhere near there.

Q. Now, Dr. McKay, based on your 40 years of experience as a surgeon and as a treater of rhinitis and considering what you have heard from plaintiffs and their theory about Barr's -- well, Nasacort AQ, first, would deposit on the frontal sinus, do you agree with their theory?

A. No, I don't. I do not believe that Nasacort AQ would deposit on the frontal sinus.

Q. Okay. And have you seen any evidence whatsoever that Barr's ANDA product enters on the frontal sinus?

A. No.

MR. GRACEY: Your Honor, at this point, we are doing both our non-infringement and our obviousness case, so Dr. MacKay is also being tendered to discuss secondary contributions of nonobviousness, just by way of roadmap.

So if we could have the next slide, please.

BY MR. GRACEY:

Q. **All right. Dr. MacKay, did we ask you to give us some opinions on whether Nasacort AQ met a long-felt, unmet medical need?**

A. **You do.**

Q. **And do you believe Nasacort meets any long-felt, unmet medical need?**

A. **No, I don't.**

Q. **And why is that?**

A. **Because we already had at least Flonase. I should just add at this point that Flonase in the United Kingdom is called Flexonase. So if I occasionally call it Flexonase, you will know why.**

Q. **Are they the exact same?**

A. **It's identical.**

Q. **All right.**

A. **It is an identical product, fluticasone propionate, with the same excipients in the same percentages. But Flonase -- we, in the United Kingdom, we actually had Flonase since 1991. So it's a long experience with it.**

Q. **All right.**

A. **And it was a once daily dosing. It was an aqueous suspension. It was safe. And it was effective.**

Q. **Now, one of plaintiffs' theories is that the difference, for instance, between Flonase and Nasacort AQ is Nasacort AQ has no scent and Flonase has a scent. I think we have heard some testimony that it has a rose scent. But the agreed construction of what odorless means in this case is odors which causes the user discomfort are absent?**

A. **Correct.**

Q. **With that understanding, do you believe Flonase is odorless?**

A. **No. I accept that it has a scent, but I have never -- I mean, as I say, I've been prescribing this.**

Q. **Do you agree that Flonase is odorless, knowing the parties' understanding that lack of an odor which causes the user discomfort is absent?**

A. **I do.**

Q. **Okay. Thank you. Continue on.**

A. **Did I not say that?**

Q. **Go ahead.**

A. **I think it is odorless by definition, as read by the Court.**

Q. **And why is that?**

A. **Because I prescribed literally thousands upon**

thousands of doses of Flonase and nobody has ever complained about the odor or the smell or the scent or any other similar word.

Q. All right. And are you aware of any greater patient compliance with Nasacort AQ over Flonase?

A. I'm aware of papers that suggest that there may be but there is no evidence that they are.

Q. And from your personal practice, are you aware of any greater compliance with Nasacort AQ than Flonase?

A. No.

Q. All right. Now you mentioned there are some papers that suggest there may be. Just generally, do you have any general critiques or criticisms of those papers?

A. I think they're excellent papers, and I have said that. I know many of the authors and I respect them, but there are some general problems I think with them. The first one I think is that none of the papers that are being cited use a questionnaire which has been validated.

Q. What does that mean, "validated?"

A. Validated means that it is being investigated to make sure it's reliable, and it's repeatable, and that it doesn't use words that are value laden like "does this smell bad" and things like that.

Q. Okay. Any other general criticisms?

A. Well, my other criticism is that quite a few of these

studies are done on a single dose basis. So what is said in the study is I'd like you to try one dose of A, one dose of B, and one dose of C; and then make a judgment as to whether you think it's preferred, more preferred, less preferred. And then on the basis of that, it is claimed that this may affect compliance.

Now, I can't see that this is a real life situation because in real life, you would be using these sprays on a regular basis for weeks, possibly months, possibly even years. And to say that it may affect compliance on that basis I think is unsound. Added to which, some of these papers go back to 1999, almost 10 years, and they have been saying it may affect compliance or it may affect compliance in some patients, but there is not one single follow-up trial to show that it actually does.

Q. Okay. Thank you, doctor.

Now, let's turn to the legal concept we call unexpected results. And again, responding to some of plaintiffs' claims on secondary consideration, do you believe, whether Nasacort's potency is less potent than Flonase, that it has an unexpected benefit due to its efficaciousness? Do you believe that is an unexpected benefit?

A. Well, at this point I'm going to say I'm a surgeon,

not a scientist, and I don't want to get too deeply into this sort of area. But my understanding is that it's been suggested that what was so surprising is that Nasacort aerosol was changed to the Nasacort aqueous solution and even though the dose was kept identical, it still worked.

Now, to my mind, there is nothing unexpected about that. If you don't change the dose, why would that be unexpected, particularly in view of the fact that exactly the same thing had been done with Beconase? Beconase went from an aerosol to an aqueous. And, again, we've had that in the United Kingdom since 1984. So that goes back more than 20 years. And it wasn't unexpected because they took exactly the same dose of the aerosol, turned it into a spray, an aqueous spray, kept the dose the same. Why should it have been unexpected that the results were the same?

Q. Okay.

A. I can't see anything unexpected about it. But as I say, I'm not a surgeon not a scientist.

Q. Thank you, doctor. And, lastly, we have eye symptoms. Plaintiffs claim that Nasacort AQ unexpectedly improved eye symptoms. Do you believe that that was an unexpected benefit of Nasacort AQ?

A. It wasn't an unexpected benefit of Nasacort AQ, but in some ways it wasn't an unexpected benefit of any of these because, again, the same thing was found with Flonase and

that was unexpected because when Flonase first came on the market in 1991, lo and behold, it treated eye symptoms and everybody said why should it treat eye symptoms? It seems odd because it's not supposed to have any systemic effect, so why does it help the eyes? But it has been known that fluticasone helped eye symptoms certainly since the early '90s.

Q. And just so we're clear, fluticasone --

A. Sorry.

Q. No, that's fine. Flonase both in England and America came on the market before or after Nasacort AQ?

A. Before.

MR. RICH: All right. That's all the questions I have for now. Thank you, doctor.

THE COURT: All right. You may cross-examine.

MR. RICH: Thank you, Your Honor.

CROSS-EXAMINATION

BY MR. RICH:

Q. Good afternoon, Dr. MacKay.

A. Good afternoon, Mr. Rich.

Q. Good to see you again.

A. Yes. Well, I wonder. Yes. You, too.

(Laughter.)

Q. We had a good time the last time we saw each other, didn't we?

A. **I won't forget it.**

(Laughter.)

Q. **Now, I'd like to start where you started in terms of the deposition in the frontal sinus. And you talked about this diagram. You didn't have all the arrows on it but it's the same diagram you used?**

A. **It is.**

Q. **And you talked about the opening to the maxillary sinus?**

A. **I did.**

Q. **You don't dispute that Nasacort AQ gets to the maxillary sinus. Correct?**

A. **Well, actually the first thing I might dispute is that isn't the opening to the maxillary sinus where it's labeled. It's an accessory ostium or because the actuating accessory to the maxillary sinus should be a little bit forward from there and you can't normally see it. It's underneath what is called the uncinate process.**

Q. **It's more hidden?**

A. **It's a little bit more hidden.**

Q. **But, nonetheless, you believe that Nasacort AQ or nasal sprays get to the maxillary sinus?**

A. **I think it's more likely that they get to the maxillary sinus than they get to the frontal sinus.**

Q. **That is not my question. Wasn't my question at your**

deposition, one more time, do you believe that nasal sprays get to the maxillary sinus?

A. **I think it's possible.**

Q. **Now, I want to talk about the route to the natural ostium of the maxillary sinus. And you believe it's possible that it gets there?**

A. **Yes.**

Q. **So the nasal spray -- and we're starting at the nasal vestibule.**

A. **It starts here.**

Q. **It starts there. And it enters the nose, goes between the inferior and middle turbinates?**

A. **Yes.**

Q. **Which is the same path to the frontal sinus?**

A. **Yes.**

Q. **And then goes past the location of where the frontal sinus is, the uncinate process underneath of the bulla ethmoidalis?**

A. **Actually, it come forwards. I'm helping you really because I'm saying it's more difficult.**

Q. **The maxillary sinus, to get to the natural ostium, after being sprayed in the nose, it would have to make a U-turn and then go laterally 90 degrees?**

A. **Well, it doesn't actually because what happens is it would sink down into this area here. So the gravity would**

take it down into a little sulcus, in fact. So if it did manage to get up here, maxillary activity could bring it down into this sulcus. I said I think it's actually pretty unlikely it gets into the maxillary sinus but it's not impossible.

Q. No, my question is to get to the maxillary sinus, would it have to be sprayed into the nose, make it in between the interior and the middle turbinates, past the uncinate process, make a U-turn and then turn laterally 90 degrees? That is the pathway it would have to take to get through the natural ostium?

A. Yes.

Q. And despite the 180-degree turn, followed by a 90-degree turn, you believe it can get there. Correct?

A. You keep slightly misquoting me because I mean whatever I may have said at my inquisition, the fact remains that I think it -- we discussed this at length.

Q. Would you like to hear your testimony back?

A. No, I'm quite happy. But I think all I'm saying now, and I don't think I said anything terribly different then, is I think it probably is unlikely that very much gets in there but I would accept that some does, okay? Yes, it might. It might.

Q. Even with that pathway with the U-turn and the lateral?

A. **Well --**

Q. **Correct?**

A. **Well, one of the explanations could be that there is an accessory ostium, like in this picture here, which occurs in -- actually, I said it might be more than it is, but it's going to occur in sort of between 9 and 25 percent of cases, something like that.**

MR. RICH: Actually, if I could approach, Your Honor?

THE COURT: You may. Are you sure you want to, though?

MR. RICH: We shook hands at the end.

THE WITNESS: No, no. We're friends, really. We're friends really except when we're doing this.

(Laughter.)

MR. RICH: If I could have the Jog article.

BY MR. RICH:

Q. **Now, this is an article entitled How Frequent Are Accessory Sinus Ostia. And if you look at the second page, that is exactly the question we're talking about; correct?**

A. **Yes.**

Q. **You look at the table down at the bottom, first, the summary I think actually can tell us all we really need to know:**

The prevalence of accessory sinus ostia was

determined in rhinology clinic patients and general ENT clinic controls. Overall, accessory sensory ostia occurred in four percent, seven percent of rhinology patients and two percent of controls had ASO.

So we're not talking 9 to 25 percent, we're talking 2 to 7 percent?

A. **You have shown me one paper which you haven't ever shown me before. And I actually looked it up in other places, and I can tell you that it does vary but it varies between about 9 percent and 25 percent, depending on which series you are looking at. But no one has ever shown me this paper before.**

Q. **And actually those earlier papers, the speculation in those earlier papers, the estimates, if we look at the first page, that is what prompted this study?**

A. **Yes.**

Q. **And that is what prompted them to find far less frequent prevalence of accessory sinus ostia than believed beforehand?**

A. **Yes. My only experience is that that is not true actually. I find it very frequently. So I would be surprised if that is correct. It depends on how hard you look for these things.**

Q. **Do you believe that the Journal of Laryngology and Otology is a respected journal?**

A. **Yes, I was on the editorial board.**

Q. **And they wouldn't accept it if it were not a quality article?**

A. **I know. But it doesn't mean you have to agree with everything you read in journals.**

I accept that there is going to be, if you look at the papers, because obviously I went back and I looked through all the papers myself to see, because I realized there could be some discussion about this. The figure I have thought is actually between nine percent and 25 percent. I did say I thought it was 50 percent, which is certainly a lot higher, but that was an impression.

Q. **Of course, that was the impression beforehand, and this study came after and showed a far lesser prevalence?**

A. **If you say so.**

Q. **If you look at the introduction, that's what it says?**

A. **Okay.**

Q. **I want to turn to your testimony on odorlessness.**

A. **Yes.**

Q. **Your testimony today was based on your personal experience with patients. Correct?**

A. **True.**

Q. **That's all it was based on today?**

A. **Yes.**

Q. **At the time you formed your opinion on odorlessness**

in relation to this case, with regard to prior art products, you had never asked a patient whether the smell of an intranasal steroid product was causing them discomfort. Correct?

A. Correct.

Q. But you agree that nasal irritation upon use of an INS drug would be user discomfort. Correct?

A. Yes.

MR. GRACEY: Your Honor, I want to make sure plaintiffs' counsel isn't going to veer from the claim construction.

THE COURT: I don't think either party is going to veer from the claim construction. By now I would think that should be understood.

MR. RICH: Understood, Your Honor. My previous question was --

THE COURT: You don't have to. Please, go ahead.

BY MR. RICH:

Q. This is the package insert for Flonase from the Physician's Desk Reference. Correct?

A. Correct.

Q. If you look at the page entitled A2, you testified that nasal irritation is user discomfort. Correct?

A. Absolutely.

Q. **It says, In general, adverse reactions in clinical studies have been primarily associated with irritation of the nasal mucus membranes?**

A. **Indeed.**

Q. **And burning the nose is certainly user discomfort. Correct?**

A. **Correct.**

Q. **And if you look at the adverse effects, nasal burning for Flonase has an incidence of three to six percent.**

A. **Right.**

Q. **And nasal irritation has an incidence of one to three percent?**

A. **Right.**

Q. **And if someone drops out of the clinical trial because of nasal irritation, that's also indicative of user discomfort. Correct?**

A. **Correct.**

Q. **If you look at the top, the last sentence says that less than two percent of patients. But it doesn't say zero. It says less than two percent of patients in clinical trials discontinued because of adverse events; this rate was similar for vehicle and active comparators.**

A. **Right.**

Q. **Now, the vehicle is a placebo. Correct?**

A. **Correct.**

Q. **It's the same formulation except lacking the active pharmaceutical ingredient?**

A. **Right.**

Q. **And here, both the vehicle, both the active and vehicle comparators would include phenyl ethyl alcohol. Correct?**

A. **Correct.**

Q. **You don't know of any reason that the odor of Flonase would enhance treatment compliance, would you?**

A. **No, I don't think it would be enhance it. Nor did I personally find that it interfered with the compliance.**

Q. **Well, you talked about some articles where they had a prospective questionnaire regarding potential compliance?**

A. **These are the one-dose studies.**

Q. **The one-dose studies. Right?**

A. **Yes.**

Q. **And in each of those, the prospective compliance with TAA was recorded, the patient said, I will definitely use triamcinolone acetonide, Nasacort AQ, to a much greater degree than saying I will definitely use Flonase?**

A. **Okay.**

Q. **That's correct, that was --**

A. **Yeah. But there is no statistical --**

Q. **My question is whether that was in the article?**

A. **Yes, that was in the article.**

Q. **One of your issues with those articles was a lack of validation of the instruments, the surveys. Right?**

A. **Yes.**

Q. **But you have used invalidated instruments. Right?**

A. **Well, you said that, and I don't think I have.**

Q. **Well, you were involved in a study that led to an article by Rojons Usau (phonetic)?**

A. **Yes, but it didn't involve any questionnaires, where we were measuring symptoms.**

Q. **I apologize. It was not a written questionnaire. It was just oral questions?**

A. **It was symptoms. We were measuring symptoms with a visual analog scale, and that's a perfectly acceptable way of doing it.**

Q. **Not all the symptoms were measured with a visual analog scale, were they?**

A. **Well, I am under the impression that they were. But you are probably going to tell me they weren't.**

Q. **Would it be fair to say that the question of how you are feeling overall --**

A. **Okay.**

Q. **-- is not measured on a visual analog scale?**

A. **I would regard that as a symptom, but fair enough. I can see where you are going.**

Q. **And you didn't evaluate that portion of the study?**

A. **True.**
Q. **And validation isn't required for data to be useful?**
A. **It limits one's confidence when interpreting the results. Would you agree?**
Q. **But it's more than zero confidence? You, in fact, do believe that data is useful even if it's not validated?**
A. **Yes, I do. May I just finish? Limiting confidence --**
Q. **Actually, Doctor, you may have an opportunity with your counsel. I wasn't asking about how confident you would be. I am asking whether it has value and is useful.**
A. **It's less valuable than one that's not validated. But it does have some value.**
Q. **So it's good but not the best?**
A. **Absolutely agreed.**
Q. **Another concern you had was in terms of retrospective surveying of patients to see whether they would comply?**
A. **Yes.**
Q. **That you hadn't seen a retrospective survey?**
A. **I hadn't seen a follow-on, followup.**
Q. **Let me, hopefully I can assist you with that.**
This is an article by a Dr. Naclearino (phonetic) and others?
A. **Yes.**
Q. **Could you see that?**

A. **Naclearino.**

Q. **Naclearino. It is entitled Patient and Physician Perspectives on the Attributes of Nasal Allergy Medications.**

A. **Right.**

Q. **Are you familiar with the 2006 Allergies in America study?**

A. **I don't think I am.**

Q. **Well, if you look at this article, at the page marked S12 at the bottom left, under Methods, it says allergies in America, a survey of adult nasal allergy sufferers. In that study, over 30,000 households in the United States were screened to obtain a national sample of nasal allergy sufferers.**

A. **Right.**

Q. **From those 30,000-plus households, a sample of 2,500 adults with symptomatic allergic rhinitis, nasal allergies, or hay fever and who would receive treatment, allergy treatment, were interviewed about their condition?**

A. **Right.**

Q. **As we can see here in the same paragraph.**

Now, if we turn two pages in, two pages further in, to the page marked S14. If you look in the right-hand column, it says, not the chart but in the column in the text itself, in the right-hand column of the text itself, it says, the majority, 61 percent, of patients with allergic

rhinitis reported that they stopped taking a nasal allergy medicine prescribed by their doctor because of an attribute of the medication rather than a change in their condition.

A. **Correct.**

Q. **So 61 percent of patients actually didn't comply with their prescriptions because of some attribute of the medication?**

A. **Right.**

Q. **Not just that they got better. There was some attribute of the medication.**

Of all patients, a quarter of them, 25 percent, reported stopping their prescription, their prescription nasal allergy medication, like we are talking about in this case, because of bothersome side effects. Do you have any reason to doubt that?

A. **No.**

Q. **Now, let's talk about what those side effects are.**

And now we can go back to the chart that's at the top corner. Just to be clear, these are patient reported side effects of some, most or all of the nasal allergy medications.

The most prevalent one is a drying feeling. Burning, which we talked about with Flonase, is on there, too, and bad taste is on there, too. Right?

A. **Right.**

Q. **Those are sensory attributes?**
A. **Okay.**
Q. **Like an odor that causes discomfort. Right?**
A. **But it isn't actually one of them.**
Q. **I understand that scent is not on there. But phenyl ethyl alcohol is an alcohol, and that can cause drying. Right?**
A. **Well, if you say so.**
Q. **Do you have any doubt that phenyl ethyl alcohol causes drying?**
A. **I am not totally sure about that. If you tell me it is, that's interesting. I would be interested to see the evidence for it.**
Q. **Okay. We may hear from others who are a little more sure?**
A. **Right.**
Q. **Now, in the studies that you have reviewed relating to patient compliance, patient preference, and odorlessness, among the intranasal steroids, the least preferred tasting products of those are phenyl ethyl alcohol. Right?**
A. **It isn't something I specifically looked for. If you say so, I am prepared to accept it.**
Q. **You don't contest that?**
A. **No.**
Q. **And bad taste is the fourth most prevalent reason why**

people stop using their nasal allergy medications?

A. **Yes. Not scent.**

Q. **One of the things you said in your expert report was that there are only really four kinds?**

A. **Five.**

Q. **You are right. Maybe you can help walk me through them. There is salty, sweet, sour, bitter, and is it umammi (phonetic)?**

A. **Umammi, which is monosodium glutamate. That is a primary taste.**

Q. **So burning isn't one of the taste senses?**

A. **That isn't a taste at all. It is a sensation.**

Q. **And the sensation is not taste. And bad tastes other than those four, that comes from scents. Correct?**

A. **Well, that taste -- no, I can't agree with you here. If you are trying to suggest that it's because of the smell that they don't like the taste, I don't agree with you.**

They mainly complain of a bitter taste. Now, a bitter taste is a primary taste. It's got nothing to do with smell. Flavor has to do with smell. So if you can tell the difference between lamb and beef, that's smell.

Taste is something different.

Q. **It's your testimony that the primary complaint in terms of bad taste is bitter taste?**

A. **Yeah. I am just giving an example.**

Q. **In intranasal corticosteroids, is bitter taste a common complaint?**

A. **Yes.**

Q. **I would like to show you an article. This is marked Plaintiffs' Exhibit 393. This is one of the articles you reviewed. Correct?**

A. **Yes, it was.**

Q. **And if we go and look at the chart that's in here, that's hard to read. Can we blow it up? If you look -- they have separated bitter taste and light taste here. Correct?**

A. **Right.**

Q. **And bitter taste is relatively low on the scale. Do you see bitter taste there? Could we highlight bitter taste?**

A. **Yes. Just let me look there.**

Right.

Q. **It is 15 for Nasacort AQ and 19 for Flonase?**

A. **Yes.**

Q. **But for liking of the taste, there is a statistically significant difference between the liking of the taste between Nasacort AQ and Flonase. Correct?**

A. **It says that.**

Q. **And there is a statistically significant difference in the liking of the odor between Nasacort AQ and Flonase?**

A. **Yes. The interesting thing about the odor is that for Flonase, it's called 55.**

Q. **My question is whether there is a statistically significant difference?**

A. **Do you not want me to answer --**

Q. **That is a yes-or-no question.**

A. **Is it?**

Q. **Is there a statistically significant difference?**

A. **It is.**

Q. **Okay. And then, if you turn to the end of this article, this is one of the articles you were talking about?**

A. **Yes.**

Q. **Where it says, Evaluations such as the one described here provide pharmaceutical manufacturers and clinicians with more information about sensory factors, improving upon patient satisfaction. With patient satisfaction, improved compliance and improved outcomes can be expected.**

Do you doubt that?

A. **We don't know. Maybe. It's yet to be proven.**

Q. **You testified earlier that Flonase was safe. Right?**

A. **It has an equal safety profile to Nasacort AQ.**

Q. **Including systemic side effects?**

A. **As far as I know, yes.**

Q. **But systemic side effects are safety issues. Right?**

A. **Yes.**
Q. **And Nasacort AQ does not have any systemic side effects?**
A. **Right.**
Q. **But with Beconase AQ, one of the products we have talked about already, growth is a potential systemic side effect?**
A. **Potentially one, yes. Skoner showed it is, but there is plenty of papers that didn't agree with that.**
Q. **There are plenty of papers?**
A. **Well, there are papers that disagree with it, because following our discussions, of course, needless to say, I did a considerable amount of research on the subject, and there are certainly papers which would disagree with the Skoner article.**
Q. **Do you think that there was any problem with the Skoner article?**
A. **Well, we discussed that as well. Woodell had suggested, not -- my colleague, Dr. Meltzer, Meltzer had sited Woodell's article. And Woodell had suggested that they were not age- and sex-matched. And in the actual article, they are not age- and sex-matched. But they had tried to make some reparations for that.**
Q. **But when we spoke earlier, you didn't doubt the correctness of the Skoner article?**

A. **I do accept that there is a possible question mark over growth in children with beclomethasone.**

Q. **Let's talk about Tilden and HPA axis. HPA axis is?**

A. **Hypothalamic pituitary access.**

Q. **That is a systemic side effect?**

A. **Yes.**

Q. **That is cortisol levels being depressed?**

A. **Absolutely.**

Q. **And that's a problem for --**

A. **Potentially, yes.**

Q. **A potential problem. Let me show you an article on this point. This is another Skoner article. Correct?**

A. **Correct.**

Q. **Now, if you look at the results, I would like to focus on the sentence that's highlighted already, saying, no significant differences in changes in urine cortisol-creatinine ratios were observed between TAA 110 micrograms or 220 micrograms and placebo. In contrast, the change in mean urine cortisol-creatinine ratios, ratio values for FP, and that's Flonase, were significantly lower compared with TAA 2000 micrograms and placebo?**

A. **Correct.**

Q. **So that's showing a systemic side effect for fluticasone propionate or Flonase?**

A. **Correct.**

Q. **In the conclusions, it says, in contrast to FP, in contrast to Flonase, TAA, Nasacort AQ nasal spray did not significantly affect HPA axis function when used over a two-week interval?**

A. **Correct.**

Q. **One more I would like to show you. This is an article by Wilson and others, entitled Effects of Repeated Once Daily Dosing of Three Intranasal Corticosteroids on Basal and Dynamic Measures of Hypothalmic-Pituitary-Adrenal-Axis Activity. Correct?**

A. **Correct.**

Q. **So if we look at the results section, the results say, for overnight urinary cortical excretion compared with placebo, there was a significant degree of suppression with FP, that's Flonase, but not with TAA, that's Nasacort AQ, or BDP, Beconase AQ. Correct?**

A. **Which is odd because you would expect there to be a difference with BDP if there was fluticasone.**

Q. **But this is a systemic side effect that is being shown with fluticasone propionate?**

A. **Right.**

Q. **Flonase in this paper had a systemic side effect?**

A. **In this particular paper, it would appear to.**

Q. **And that's a safety issue?**

A. **Right.**

Q. **One last line of questions.**

You talked about Nasacort AQ versus Nasacort and nasal inhaler with regard to Flonase.

A. **Yes.**

Q. **In your mind, there is no distinction in effectiveness between the 220 micrograms per day daily dosage of Nasacort AQ and the 200 micrograms dosage of fluticasone propionate. Correct?**

A. **Correct.**

Q. **And you can't explain that differential in potency between are fluticasone propionate and triamcinolone acetamine and the mere identity of effectiveness of the two drugs?**

A. **No.**

MR. RICH: Thank you. Nothing further, Your Honor.

THE COURT: Redirect.

REDIRECT EXAMINATION

BY MR. GRACEY:

Q. **Hello again.**

A. **Hello.**

Q. **Take a look at the Skoner article, the 2002 article. Have you reviewed this version of the Skoner article that plaintiffs put in front of you? It's entitled The Effects of Intranasal TAA?**

A. **No.**

Q. **And, in fact, if you will turn to the last page of that article, 61, not the last page, second-to-last page, penultimate page?**

A. **Right.**

Q. **If you will look at the acknowledgment, you will see this was a study supported by a grant by RPR?**

A. **Right.**

Q. **That is an affiliation of Aventis. Right?**

A. **It is.**

Q. **All right. He showed you a few other articles about Flonase and its safety. Right?**

A. **He did.**

Q. **And I know you practice in England, but as far as the United States goes, is Flonase still an FDA-approved drug?**

A. **It is.**

Q. **It has to be a safe and effective drug to be approved. Right?**

A. **It does.**

Q. **Is it still approved in England?**

MR. RICH: Your Honor, this is beyond the scope of cross.

THE COURT: Overruled.

THE WITNESS: The answer is, it is approved in

the United Kingdom, yes.

BY MR. GRACEY:

Q. Now, he also asked you some questions about odorlessness?

A. Yes.

Q. Odorless is a term of art for this case?

A. I understand.

Q. That, I think you testified earlier, it's an odor that causes patient discomfort is lacking?

A. I understand that.

Q. If we could pull up the PDR, the '95 PDR. DX-16.

Now, plaintiffs have identified nasal burning, and nasal irritation. Nasal burning is not odor, is it?

A. It is not.

Q. And nasal irritation, is that odor?

A. No.

Q. Is bad taste the equivalent of odor?

A. No.

Q. Now, plaintiffs' counsel asked you some questions about the entrance to the maxillary sinus. Do you remember that?

A. I do.

Q. And he was quarreling with you about what percentage if it gets into the maxillary and what not. Even if you

take him at his word about the four to seven percent, I think was the number, does that have anything to do with the ability of a drug to get into the frontal sinus?

A. Not at all.

Q. Is it your opinion that it is easier or more difficult to get to the maxillary sinus than the frontal sinus?

A. Well, it's considerably easier for me to get to the maxillary sinus as a surgeon. But I think if you are talking about a spray, it would definitely be, it would definitely be easier to get to the maxillary than to the frontal by a magnitude of a hundred.

MR. GRACEY: That's all the questions I have, Doctor.

THE COURT: You are excused, Doctor. We will take a break.

(Witness excused.)

(Recess taken.)

THE COURT: All right. Please be seated. Your next witness.

MR. HURST: Your Honor, our next witness is Maureen Donovan.

THE COURT: What is the first name?

MR. HURST: Maureen. Dr. Maureen Donovan.

- - -

DEFENDANT'S TESTIMONY

... DR. MAUREEN DENISE DONOVAN, having been placed under oath at 3:25 p.m. as a witness, was examined and testified as follows ....

- - -

THE COURT: Good afternoon.

DIRECT EXAMINATION

BY MR. HURST:

Q. **Dr. Donovan, how are you currently employed?**

A. **I work at the University of Iowa. I'm an associate professor there.**

Q. **Associate professor in what?**

A. **In the College of Pharmacy is where my primary appointment is.**

Q. **How long have you been in Iowa?**

A. **I've been there 19 years.**

Q. **Just as background, can you describe for Judge Sleet your educational background?**

A. **I have a Bachelor's Degree in Pharmacy from the University of Minnesota and a Ph.D. in Pharmaceutics from the University of Michigan.**

Q. **And when did you get the first degree? What year?**

A. **In 1983.**

Q. **Okay. And when did you receive your Ph.D. from the University of Michigan?**

A. **In 1989.**

Q. **I apologize. Both in Pharmaceutics. Correct?**

A. **Well, my bachelor's degree in Pharmacy and my Ph.D. in Pharmaceutics.**

Q. **So after you got your Ph.D. in 1989, where did you go then?**

A. **I took a position as an assistant professor at the University of Iowa.**

Q. **As?**

A. **As assistant professor in the College of Pharmacy.**

Q. **And you have been there ever since?**

A. **Yes, I have.**

Q. **Do you teach courses as a professor at Iowa?**

A. **I do. I teach courses to pharmacy students and I teach courses to graduate students in the pharmaceutics program across the campus.**

Q. **Just generally, what kind of courses do you teach?**

A. **The courses I teach to our pharmacy students are use of formulations and relative administration of drugs for typical how pharmacy would view them. So how to treat suspensions and solutions properly, how people need to use tablets or patches, so sort of the gamut of dosage forms and their designs in general and their proper use.**

Q. **And if you said this, I apologize. That's both graduate students and undergraduate students?**

A. **My focus is the undergraduate students or professional students for that course. I have a course in drug delivery systems that I teach graduate students, and that course is more focused on design of delivery systems and various routes of delivery, the limitations at those routes perhaps and the number of the materials you would choose for formulation at one route vs. another route.**

Q. **Do you conduct research at the University of Iowa?**

A. **Yes, I have a funded research laboratory that I run at the university.**

Q. **How long have you been conducting research at Iowa?**

A. **Again, about 19 years.**

Q. **Okay. Generally, what kind of research is this laboratory research?**

A. **Yes.**

Q. **What kind of research do you conduct at Iowa and have you been conducting at Iowa?**

A. **The majority of the time I've been there, I had a research focus on nasal drug absorption, nasal drug delivery, optimization of nasal dosage form. I look at other routes of delivery, too, but most of the work has been focused on nasal drug formulations.**

Q. **All right. Do you publish articles? Have you published articles?**

A. **Yes, I have.**

Q. **Approximately, how many?**
A. **Over 40.**
Q. **Of the 40 articles that you published, how many actually relate to nasal formulation issues and nasal products?**
A. **Probably, at least three quarters of them.**
Q. **We've heard some testimony in the case that pharmaceutical formulators don't, by themselves, create and make pharmaceutical formulations. Have you heard that?**
A. **I've heard that, yes.**
Q. **Are you a pharmaceutical formulator?**
A. **Yes, I am.**
Q. **Have you, by yourself, on your own made pharmaceutical formulations?**
A. **Yes, I actually have.**
Q. **And how often have you done that?**
A. **Well, I think I do it a lot, to tell you the truth.**
Q. **Do you sometimes ask your graduate students to create, by themselves, pharmaceutical formulations?**
A. **Yes, I do.**
Q. **Now, how long has your focus as a pharmaceutical formulator been on nasal delivery of drugs? Delivery of drugs through the nasal passages.**
A. **It's been longer than the time I've been at the university much Iowa. So it's approaching 23, 24, 25 years.**

My graduate Ph.D. work was in looking at nasal absorption. We looked at comparative absorption between the nasal cavity and the gastrointestinal tract. And so I started my work in nasal delivery about the same time or shortly after I entered the graduate program at the University of Michigan.

Q. **As a pharmaceutical formulator who focuses on nasal issues, do you study the viscosity of the formulations you are working with?**

A. **Yes, I do.**

Q. **What kind of study of viscosity do you do?**

A. **We looked at viscosity probably as one of the significant focuses in my research for at least the last 10 years. And I've been trying to find materials or identify characteristics of materials that will help retain them in the nasal cavity; and viscosity profile being one of the ways, one of the aspects of the materials that I'm looking at.**

Q. **Okay. As a pharmaceutical formulator who focuses on nasal formulation, do you also study the pattern of nasal deposition?**

A. **Yes, I do.**

Q. **Within the cavity?**

A. **Yes.**

Q. **Can you explain for Judge Sleet what kind of work have you done in that area?**

A. **Sure. We have done mostly in vitro work in an MRI-derived model. And so somebody took an MRI of a human, a live human's nasal cavity and that was machined, the measurements and so forth, of the inside of the nasal cavity. So sort of that complicated structure you saw on some of Dr. MacKay's actual head diagram has been machined through plexiglas into a model, that we then spray materials into to try to see whether those materials go, and not necessarily -- we can look at a little bit about where they're retained, but it's not the best model for looking at. We can't look at mucociliary clearance, obviously, but we've spent a lot of time looking at formulation issues and device issues that determine where the spray is going.**

Q. **Over your 20 years in this area, have you gained an understanding of the nasal anatomy?**

A. **Yes, I have.**

Q. **Is that important to your work?**

A. **Yes. Again, because we're interested in characterizing drug absorption, optimizing drug absorption for the nasal cavity, I need to know, again, how to get the materials to the site I'd like them to go to for their activity. And so I need to know the aspects of the nasal anatomy that play a role in determining how to get the drug to the site I wanted to.**

Q. **How specialized is it? How common is your focus on**

nasal formulation products and research devoted to nasal products? Is that something that a lot of people do?

A. Not very much. Maybe 10 people.

Q. Okay. In the United States or worldwide?

A. That's probably even fair worldwide. People who have that specific a focus, it's very few.

Q. Okay. Is one of the other folks who spoke who focuses on nasal formulations in the courtroom?

A. Yes. As a matter of fact, he is.

Q. Who is that?

A. That is Dr. Needham.

Q. And he is sitting behind Barr's bench?

A. Yes, he is.

MR. HURST: Your Honor, I'd like to proffer Dr. Donovan as an expert in pharmaceutical formulations with special expertise in how drugs are delivered to the nasal passages.

THE COURT: Any objection?

MR. BERGHOFF: No.

THE COURT: The doctor is accepted as such an expert.

BY MR. HURST:

Q. Dr. Donovan, yesterday you saw Dr. Kaliner do an in-court demonstration where he sprayed nasal spray in the air and it formed a plume or a cloud?

A. **Yes, I saw that.**

Q. **All right. Is that an accurate representation of what actually happens when a nasal spray is sprayed into the nasal cavity?**

A. **No, that cloud doesn't form within the nasal cavity.**

MR. HURST: Your Honor, with your permission, we wanted to do an entirely low-tech drawing just to help describe what actually happens when a nasal spray goes into the nasal cavity. So can I ask Dr. Donovan to do a little handwritten drawing on the Elmo?

THE COURT: Sure.

THE WITNESS: If I speak like this, can you hear me?

THE COURT: You're fine.

THE WITNESS: Fine? All right.

THE COURT: I can tell you are a teacher.

THE WITNESS: What I'm going to draw is, are two nostrils. And the perspective is if you are looking up someone's nose, okay?

So the bridge of your nose is coming down here (indicating).

BY MR. HURST:

Q. **Take a look up there.**

A. **Oh. I needed to sort of step back while I was doing that.**

Q. **Yes. Now, describe what you are doing.**

A. **This is one nostril, that being the other nostril. And this part of your nose, basically the tissue part, is in between.**

Q. **Okay. And just to help orient, is there like a tube straight back to the nasal cavity from the opening in the bottom of the nose?**

A. **Not a straight tube.**

Q. **Okay.**

A. **What you see, when you look up the nostrils; if it's lit up, you can see a little bit more; but the nostrils are actually a relatively large opening and the airway is narrow. And we heard about that yesterday actually, Dr. Kaliner talked about the nasal valve which is behind the area where the hairs in the nose are, right where we're getting that transitional epithelium area that Dr. MacKay was just talking about.**

That nasal valve area, in addition to having some changes in the cell types, is a narrowing in the air space. Okay? And so as you look up, you kind of see sort of an oval boot-shaped kind of area. And that is really the keyhole that the spray is going through. Okay? So we put the nozzle into the nasal cavity or into the nostril and actuate it and the spray starts to form this, but it's facing sort of a viaduct.

THE COURT: "This" meaning going out?

THE WITNESS: Yes. As we saw the spray yesterday, it formed the nice plume; right? Well, when it's in your nostril, it starts, it tries, but about a centimeter in front of it or so, depending on how far you have it up your nose, it meets this narrowing area. So a lot of the spray actually ends up depositing right here. And just the portion that is in line with this area -- and you can see my hand -- that the X area is that opening nasal valve narrowing opening. That it's only a fraction of the spray that passes through the keyhole that gets into the nasal cavity and back to the turbinates.

THE COURT: So, counsel, do you want to have her indicate for the record what she just did?

MR. HURST: Just describe?

THE COURT: Well, the marking she just made.

MR. HURST: Thank you.

THE WITNESS: Okay. Do you want me to label them? Would it be helpful?

THE COURT: You can orally describe it.

MR. HURST: Orally describe so it appears on the record what you have just drawn.

THE WITNESS: All right. What I have drawn is an elliptical shape that represents the nostrils. And then within that, and meant to be in perspective behind that, is

another sort of elliptical shape that has a smaller dimension, usually maybe half-to-three-quarters of an inch in length and a quarter of an inch in width or so. That is the nasal valve region. The airway narrows there. And so when we're trying to send a spray that is forming a plume into the main nasal cavity, only the part of the plume can go through that inner elliptical shape. And the material that I have tried to -- that the lines that I have on the outside are actually spray that couldn't get through the keyhole, so it ended up on those tissue surfaces, and only a fraction of the spray went into the nasal cavity. And --

MR. HURST: Go ahead.

THE WITNESS: And then I'm not going to draw this. And if you need to, we can pull up another visual, but you remember Dr. MacKay talking about the front end of the turbinates.

THE COURT: I do.

THE WITNESS: That is where most of the spray ends up after it passes through the nasal valve.

BY MR. HURST:

Q. Thank you, Dr. Donovan.

A. (Retakes witness stand.)

Q. While this drawing is still up, is there any more narrow part of the nasal cavity than the nasal valve?

A. No, not for the total airflow going through that, the

nasal cavity region.

Q. **So when the nasal spray goes through this keyhole, as I think you described it, does it reform a plume?**

A. **No, it does not.**

Q. **What happens?**

A. **Now, whatever is traveling through the nasal valve is now suspended in the air stream. And, again, if it can't curve around the turbinates, if it can't go into the meatuses between the turbinates, well, then it has impacted on to the surface of the turbinates. So either it's light enough that it can stay floating in the air stream and travel as the air is traveling and through the meatuses again and over turbinates or it hits on the surfaces and stays there.**

Q. **Well, did the spray droplets from the nasal spray, do they bounce around the inside of the nasal cavity?**

A. **No, this is sort of line raindrops on the floor. When they hit, they splat and they may spread. They probably do. They don't bounce back off.**

Q. **When they hit, they stick?**

A. **Yes, when they hit, they stick.**

Q. **Why don't we take a look at Defendant's Exhibit 5? You have seen this report before?**

A. **Yes, I have.**

Q. **This is a PET study that Dr. Berridge did in 2002.**

Correct?

A. **Yes.**

MR. HURST: Your Honor, my apologies. I have a binder. It's not many exhibits. May I approach?

THE COURT: Yes.

BY MR. HURST:

Q. **Take a look at, if we can, Page 12 of this exhibit. Now, you have seen this depiction of the results from the 2002 study before. Correct?**

A. **Yes, I have.**

Q. **You are not a PET scan expert, are you?**

A. **No.**

Q. **My only question for you then, Dr. Donovan, is what is your reaction to this deposition pattern as a person who is skilled in nasal formulations and has studied deposition patterns?**

A. **It's exactly the deposition pattern I would expect.**

Q. **Why do you say that?**

A. **That the area that's referred to as nasal regions is that nasal valve before the turbinate region, again, so that's what I call the anterior region, that's where you expect the highest deposition. And that's exactly where the highest deposition of this, both Flonase and Nasacort showed up.**

There is some deposition in the turbinate

region, it is certainly expected, especially on those anterior surfaces of the turbinates. And there is absolutely no deposition in the frontal sinus, which is exactly what I would expect.

Q. Now, you have been in the business of making nasal formulations for 20 years. Today, Dr. Donovan, today, 2008, do you know how to make a nasal formulation that's capable of reaching the frontal sinus?

A. No, I don't.

Q. Well, you did read both the patents that are at issue in this case, did you not?

A. Yes, I did.

Q. Did you study them?

A. I did.

Q. Did they teach you, as a person who focuses on making formulations in this area, how to make a nasal formulation that is capable of reaching the frontal sinus?

A. They did not. I looked at the example in the patents, and looked at the materials in that, looked at the information about the formulation. And there is nothing unique about the formulation components, there is nothing unique about the spray device, there is nothing about the spray characteristics that would help me understand that this would be able to deliver something to the frontal sinuses. So I can't discern anything from the information

provided in the patent as to how the material is able to deliver drug to the frontal sinus.

Q. Now, you have offered an opinion in this case relating to the enablement issue. Correct?

A. Yes, I have.

Q. Just very briefly, because we are going to spend some time on it, what is your opinion -- let me ask you this: Did you offer that opinion from your own perspective as a person with 25-plus years in this area, or from the perspective of one of ordinary skill in the art?

A. No. I was asked to offer that opinion based as someone of ordinary skill in the art at the time of these patents.

Q. So let's --

THE COURT: Have we identified that person of ordinary skill in this record?

MR. HURST: This would be the first time, Your Honor.

THE COURT: She is going to provide that information?

MR. HURST: Yes.

BY MR. HURST:

Q. Let's talk about that issue. What is the general subject matter of the patents?

A. They describe a nasal formulation, a formulation that

contains a corticosteroid as the active ingredient. And more specifically about these, these actually describe the reformulation of a nasal steroid.

Q. **Why do you say reformulation?**

A. **Well, because there was a product that was administered, triamcinolone acetonide, prior to these patents. It was delivered as a propellant-driven aerosol. And these describe an aqueous nasal spray. So it's a change in formulation but not a change in drug and not a change in route of administration.**

Q. **Do you have an understanding of the type of education and experience one might have as of 1996 in terms of formulating a nasal spray?**

A. **Sure. I know a number of formulators. I knew them then. And they have a broad range of experiences. Usually, they have a Bachelor's degree.**

Q. **One second. I want to make sure that you have a foundation for actually describing this. You were doing this in 1996?**

A. **Yes, I was.**

Q. **You were in academia. Did you have contacts with industry?**

A. **I did. I had worked in industry for short periods of time. I trained students who went out and worked in industry. I had contracts from people in the industry to**

work on nasal formulations. So I knew very well the kind of people that were acting and developing nasal formulations and their backgrounds.

Q. Let's take it a step at a time. How about level of education, for folks who were actually doing nasal formulation work in 1996. Just level of education?

A. Bachelor's degrees, Masters degrees, Ph.D.

Q. What subject matter of education, what kind of education is most useful in this area?

A. My perspective is the most useful background is, a long time ago it would have been pharmacy. Now it's turned into pharmaceutical sciences just because of how pharmacy education works.

That's most suited, because the individuals know about the materials, they know about the physiology, the biology, and so forth. There are lots of other backgrounds that people have for formulators, however. So there are biologists by training, chemists by training, chemical engineers by training, biochemists by training.

So there is a fairly broad biomedical or basic science background that formulators have.

Q. Do those folks who don't actually have pharmaceutical sciences degrees, do they need any extra training before they actually do pharmaceutical formulation work?

A. I believe they do. And the ones I am associated with

have some sort of training experience in pharmacology and in physiology and in anatomy and in material sciences regarding safe and effective materials to use in pharmaceutical formulations.

So it is their way of getting the body of knowledge they didn't get by not being in a pharmaceutical sciences program.

Q. So how many years of experience, of actual pharmaceutical formulation work would be required, in your view, to be an ordinarily skilled pharmaceutical formulator in 1996?

A. Well, if somebody had a Bachelor's degree in any of the areas I talked about in 1996, in addition to that, they probably need maybe three to five years of direct formulation experience and even direct experience formulating nasal dosage forms to be considered skilled in the art and able to independently develop their nasal formulation.

If it was somebody with a Master's degree, they would have a little bit more didactic training, so maybe they need a little bit less than experience, three years or so. Then again a Ph.D. People who have more training and more scientific background need a little less on-the-job training, perhaps. But they still would have to become experienced in nasal formulation development in order to be

able to do this on their own, to the best of their abilities.

Q. Aventis has suggested that one of ordinary skill in the art would actually be a team that included a medical doctor. Just in your experience with pharmaceutical formulation, is that really part of the definition of one of ordinary skill in the art?

A. For formulation development, no. Somebody does not have to be a medical doctor or necessarily even interact with somebody who is a medical doctor to formulate a dosage form.

Q. How about in this particular case, where you were working with an active ingredient that was an old active ingredient?

A. Especially in this case, again, this was a reformulation, an agent that had been shown to be effective and safe, and the intent for treatment was the same. There would be very little role, in fact, probably no role for a trained medical person to do anything regarding the formulation itself.

Q. Okay. So now, with that definition of one of ordinary skill in the art in mind, what is your opinion with respect to whether or not these patents teach an ordinarily skilled formulator how to make a nasal spray that reaches the frontal sinus?

A. **I don't think they teach someone of ordinary skill in the art how to reach the frontal sinus.**

Q. **Why do you say that?**

A. **Well, as I said before, they don't teach me how to reach the frontal sinus. In 1996, I was a person of ordinary skill in the art. And they didn't teach me, they wouldn't have taught me that in 1996. They don't teach me it now even.**

Q. **Is there any unique ingredients that are used in a claimed formulation that might make it more likely to reach the frontal sinus?**

A. **No. These are ingredients that were used in other nasal formulations.**

Q. **Such as?**

A. **Well, again, Beconase AQ, Flonase, use the same ingredients. And I am not aware that they get to the frontal sinus. And I don't know how this material, if it gets to the frontal sinus, does it, and there is nothing in the patent that describes how to accomplish that.**

Q. **After reading the patents, if your assignment was make a nasal formulation that reaches the frontal sinus, would you even know where to begin?**

A. **No.**

Q. **Let's take a look at Defendant's Demonstrative Exhibit 15.**

We have looked at this before. The frontal sinus, we have looked at this so many times, Judge, I am not going to belabor it. You see the frontal sinus there on the left.

A. **Yes, I do.**

Q. **Is the frontal sinus an area of interest for your average nasal formulator?**

A. **No.**

Q. **Why not?**

A. **Because the average nasal formulator, a person skilled in the art knows that you cannot get to the entrance to the frontal sinus to use that as a pathway into the frontal sinus from the nasal cavity.**

Q. **Now, in all your years of experience, in this area of study, have you ever heard, have you ever heard of a nasal spray that reliably reached any of the sinuses much less the frontal sinus?**

A. **No, I haven't.**

Q. **Do you think, given your area of research and focus, that you would have heard of such a development in the progression of nasal sprays?**

A. **Yes. If there was a way to use the nasal cavity to deliver something to the frontal sinus, I would know about it.**

Q. **Now, outside the context of this particular case --**

let me ask you this: Are you familiar with Nasacort AQ?

A. **Yes, I am.**

Q. **Have you been familiar with Nasacort AQ even before you got involved in this case?**

A. **Yes, I was.**

Q. **Had you heard of anybody claiming that Nasacort AQ could reach the frontal sinus until we approached you in connection with this case?**

A. **No, I don't recall hearing anything about Nasacort AQ reaching the frontal sinus.**

Q. **Okay. Let's take a look to a different issue now. We will finish with enablement and go to an infringement issue. Claim 5, we are looking at DX-7 at 10, Claim 5.**

Now, just to orient ourselves, do you see where it says shear viscosity, it's actually shear shaken, II?

A. **Yes.**

Q. **It talks about a viscosity of 50 to about 200 centipoise?**

A. **Yes, I see that.**

Q. **We asked you, did we not, for your opinion on whether a nasal spray, and in particular Barr's product, would actually go from 50 to 200 centipoise back up to 400 to 800 centipoise after being delivered to the nasal cavity. Correct?**

A. **Yes, you did ask me about that.**

Q. **And what is your opinion on whether or not Barr's product returns to that 400 to 800 viscosity level after being deposited in the nasal cavity?**

A. **My opinion is that the environment to the nasal cavity is so totally different than the measured value on the bench top that we have been hearing about, and most of the aspects are going to adversely affect its ability to return to 400 to 800, that I don't think it can. I don't think it can reach 400 to 800 once in deposited form.**

Q. **Let's take a look at Defendant's Exhibit, Demonstrative Exhibit 54. This is something that you have worked with to help explain your opinion on this issue?**

A. **Yes.**

Q. **First, is there a temperature difference between laboratory testing and the temperature in the nasal cavity?**

A. **Yes, there is nearly a 30-degree difference.**

Q. **And can that make any difference with respect to viscosity?**

A. **Certainly. And most materials I have worked with, that over a 30 degree span, you see a difference in their viscosity.**

Q. **Which direction is that?**

A. **Most materials, the viscosity decreases as the temperature increases.**

Q. **So we are going the opposite direction?**

A. **Yes, we are.**

Q. **How about dilution, when you are doing tabletop testing, is there any dilution?**

A. **No.**

Q. **How about within the nasal cavity, is dilution occurring?**

A. **Yes. Because once that spray enters the nasal cavity and deposits on the surface, it interacts with the mucus that's there and the other secretions. We heard, there is a lot of secretions, a large volume actually of secretions actually during the day that go through the nasal cavity. So the formulation that you just put in there gets diluted by those secretions.**

Q. **What does that do to viscosity?**

A. **Again, it drops -- it's a polymer, the carboxymethyl cellulose, the microcrystal cellulous Avicel is a formulation that induces the viscosity behavior, so that gets diluted out and as a result the viscosity is different and it's less.**

Q. **Aventis has suggested there won't be any mixing between the nasal spray and the nasal fluids. You heard that testimony?**

A. **I heard something to that effect, yes.**

Q. **Do you agree with that?**

A. **No, I don't.**

Q. **Why not?**

A. **Well, I believe that when this formulation enters the nasal cavity, it impacts on the mucus, and may interact with the mucosal surface, and the mucus and the formulation are going to interact and they are going to mix. And the Avicel polymer system is going to be able to interpolate into the mucus and the water from the mucus is going to be able to enter the formulation. And the drug that is dissolved in the formulation is going to be able to move within the whole mixture.**

Q. **So in the formulation itself, is it water-based?**

A. **Yes.**

Q. **Is mucus water-based?**

A. **Yes, it is.**

Q. **How much mucus is water?**

A. **Mucus is about 95- to 97-percent water.**

Q. **So the fact that the formulation is mostly water, the fact that the formulation is aqueous-based and that mucus is mostly water, does that advise you on whether or not there would be a dilution of the formulation once it reaches the nasal cavity?**

A. **Certainly, I think, you know, the water is free to move between those two materials, starting materials. It diffuses between, among them. So, yes. Being both water-based, being both almost entirely water, really, by**

composition, is going to allow them to easily mix.
Q. Now, have you seen any testing from Aventis to attempt to measure the impact of interaction between mucus and Barr's product with respect to whether or not Barr's product meets III of Claim 5?
A. No. I see no testing on Barr's product. I actually see no testing on Aventis's product regarding what its return to -- what its viscosity is in the nasal cavity.
Q. I forgot to mention with temperature, you mentioned there was a difference, potentially a difference in viscosity when you are talking about room temperature versus body temperature. Right?
A. Yes.
Q. Have you seen any testing in this case relating to whether or not Barr's product would actually, how quickly it would return to setting viscosity, if at all, at 98.6 degrees?
A. No, I haven't seen any of those results.
Q. Let's talk a little bit about No. 3, constant ciliary. Why don't we start on the left. Is there any disturbance when you are measuring viscosity on the tabletop?
A. Again, as long as you have set the experiment up not to have it disturbed, there is no disturbance, yes.
Q. Is that also true in the nose?

A. **Absolutely not.**

Q. **What happens in the nose?**

A. **Well, numbers of people enjoyed that video yesterday and so did I. The cilia beating are going to be interacting with the material that they are interfacing with, mucus formulation, and as a result, any formulation that directly interacts with the cilia is going to be sheared by those cilia. And we know that these formulations shear thin, that it's thixotropic, that it decreases in viscosity under shear forces. So cilia, if it has a chance to just interact with the formulation, will shear the formulation.**

The mixed formulation mucus is already a lower viscosity to begin with because it's been diluted. The cilia are still interacting with that, also shearing, and likely keeping the viscosity low.

Q. **We heard earlier today that what really happens is there is that mucus blanket on top of the cilia, and so, sort of like a roller at an airport, I think, where it's a conveyor belt, the mucus is a conveyor belt with a composition that sits on top without interacting. Did you hear that testimony?**

A. **I heard that, yes.**

Q. **Is that an accurate description of what actually happens in the nasal cavity?**

A. **Not regarding this formulation.**

Q. **Why do you say that?**

A. **Again, this formulation has the capability of interacting within mucus. The polymers can interact, the drug can diffuse from the formulation into the mucus. And so if it was just being escalated out of the nasal cavity, the drug would have no effect, because it has to get to the cells below the mucus blanket and maybe even into other parts of the sub-mucosal tissues to have its effect. If it is just being transported out, it can't be what's going on.**

Q. **Let's explain that and expand on that a little bit. If the conveyor belt system was really what was happening, these suspensions, these products, are designed to suspend drug particles. Right?**

A. **Yes, they are.**

Q. **And so if it was a layer like this, the composition on top of mucus blanket, with the cilia providing a conveyor belt, where would the drug particles be going?**

A. **They wouldn't be going anywhere. I mean, they would be going out the nasal pharynx along with the mucus blanket.**

Q. **So if that was the case, if there was just a conveyor belt conveying the drug particles out of the nasal cavity, without any shearing or anything like that from the cilia, what would the effect of the drug be in terms of helping to treat the disease?**

A. **Again, you would lose almost the entire dose of drug**

that you put in there. So you would have very little effect, because it was conveyed out by that picture that was painted, just the material would be relatively ineffective, because you have moved most of the drug particles away from their site of activity.

Q. So, then, if it's not a conveyor belt, does the cilia -- how fast does it beat? We have heard. A thousand beats a minute.

Does the cilia in the nose have a tendency to reduce the viscosity of nasal sprays, in your opinion?

A. In my opinion, yes, those are forces on those materials and they cause them to be reduced in viscosity if they are capable of reducing in viscosity under shear.

Q. Finally, the last one is constant breathing, sniffing, and turbulent air. Is the nasal environment a static, calm environment?

A. Absolutely not.

Q. Why not?

A. Well, we have heard once you get into that turbinate region, the air flow is turbulent in the turbinates. It swirls around. It's trying to contact the mucosal surfaces, basically, so they can do that heat and water exchange physiologically.

But just by the air moving, people sniffing, causing greater velocities and so forth, it is not an

undisturbed surface, particularly likely with somebody with rhinitis who has lots of congestion and is sniffing, it is not going to be undisturbed at all.

Q. Just to sum up, what is your opinion with respect to whether Barr's product would I guess nearly double in viscosity while in the nasal cavity during the time that it's in there?

A. Again, the residence time is so short in the nasal cavity, I do not believe that it is able to return to its setting viscosity while it's there.

Q. And in your review of the evidence in this case, have you seen any testing from Aventis that attempted to mimic all of these factors together, much less even one of them, in trying to prove that Barr's product did, in fact, return to setting viscosity in the nasal cavity?

A. No, I have seen no data that tries to replicate anything that might occur in the nasal cavity to determine what the viscosity in deposited form would be.

MR. HURST: I have no further questions right now. Thank you, Your Honor.

THE COURT: You may cross-examine.

MR. BERGHOFF: Thank you, Your Honor.

CROSS-EXAMINATION

BY MR. BERGHOFF:

Q. Dr. Donovan, I apologize. I have not introduced

myself to you yet in this case. I am Paul Berghoff. It's nice to meet you, and I will shake your hand when we are done.

A. **It is a pleasure to meet you.**

Q. **Now, Dr. Donovan, I believe you mentioned in describing your qualifications as an expert that the viscosity of nasal spray formulations is an important part of your research?**

A. **The viscosity of nasal formulations or components of nasal formulations is an important part of my work, yes.**

Q. **That is true today and has been true for about how long?**

A. **At least ten years.**

Q. **And the goal of your research, as I understood it, as it relates to viscosity, was to understand or to assist the retention of nasal spray formulations on the mucosal surfaces?**

A. **Well, we are trying to understand the material characteristics that would allow that to happen, that would allow increased residence time in the nasal mucosa.**

Q. **And in terms of the viscosity characteristics that you studied for nasal formulations, currently and over this decade-plus period, have you looked both at setting viscosities and at sheared viscosities? And let me just say, you have probably heard, these are loaded terms defined**

by the Court. I am not using them in that sense. Just in an ordinary sense, setting viscosity or shear viscosity.

A. Setting viscosity and sheared viscosity that we have been dealing with here are not the viscosity characterization techniques that I use to study the materials that I am interested in.

Q. But you do recognize those terms?

A. By the definitions, yes, I do.

Q. And you referred to the shear viscosity formulations, nasal formulations in general in at least your first expert report, did you not?

A. Yes, based on the definitions that were used in the patent.

Q. And it's your view that the shear viscosity of nasal spray formulations is usually more significant than the unsheared viscosity?

A. Yes, that was my opinion.

Q. Now, you testified this afternoon about the issue that we've heard other witnesses on this, what gets to the frontal sinus?

A. Yes.

Q. And it's your view that it's not impossible that some component of a nasal spray may deposit in the frontal sinus. Isn't that correct?

A. Well, similar to Dr. MacKay, I think it's incredibly

unlikely. It would have to be a very unique characteristic of a portion of a nasal formulation that could be able to get there. Again, I'm a scientist so I have a really difficult saying anything is impossible, but I can think of very few aspects of anything that would allow them to get to the frontal sinus via a nasal spray.

Q. **And during -- I'm trying to save time rather than go through putting the deposition testimony up. But during your deposition, you testified you didn't think it was impossible that some component of a nasal spray may deposit on the frontal sinus?**

A. **That's right. I said some component may deposit in the frontal sinus, but I thought it was unlikely.**

Q. **And in the two expert reports that you submitted in this case and in your testimony this afternoon, you have offered no testing of your own concerning deposition in the frontal sinus; is that correct?**

A. **No.**

Q. **That's not correct or --**

A. **No.**

Q. **-- you offered no testimony?**

A. **I did no testing of my own.**

Q. **That was a problem with my question, not your answer. I just wanted to make sure it was clear.**

Now, Dr. Donovan, you talked about the cilia?

A. **Yes.**
Q. **And shearing the nasal spray formulations?**
A. **Yes.**
Q. **But it's correct, isn't it, that you are not aware of any data that demonstrates that the cilia altered the viscosity of the deposited nasal product through shear forces?**
A. **I am not aware of any data, any experiments where people have been able to measure the viscosity of a formulation in a deposited form in the nasal cavity.**
Q. **And you testified about Avicels, I believe, and my memory is it was during the section of your testimony that you were talking about the supposed dilution of a nasal spray formulation in the nose?**
A. **Right. I brought the Avicels in, yes.**
Q. **In fact, you have not worked with any thixotropic systems based on the use of Avicels, have you?**
A. **No, I haven't used the particular grade of Avicels that we have been referring to in these formulations.**
Q. **In fact, you haven't used any grade of Avicel?**
A. **Not in nasal formulations, no.**
Q. **Now, Dr. Donovan, on the enablement issue, I believe your testimony was that if you were asked to develop a nasal spray formulation that deposited in the frontal sinus, you wouldn't even know where to begin. Is that a fair --**

A. That's fair.
Q. -- a fair summary of what you said?
Now, I want you to assume that Dr. Berridge's test data -- and you are aware of Dr. Berridge's test data, aren't you? You were here when he testified.
A. Right. In all, I think he completed three tests. Do you want me to include all of those or is there a specific test you would like?
Q. No. As Dr. Berridge testified, you can leave the 2002 aside. I'm going to ask a much simpler assumption for you to make just so you don't have to think about all the particular data. I just want you to assume that Dr. Berridge's conclusion that there is deposition of Nasacort AQ in the frontal sinus is correct. That's the assumption.
A. Okay. If I assume that is correct, yes.
Q. So if that is true, then the patents in suit do indeed disclose the exact formulation of a nasal spray product that will deposit in the frontal sinus. Correct?
A. If I believe that Dr. Berridge's data is correct that Nasacort AQ deposits in the frontal sinus, then, yes, the formulation for Nasacort AQ is disclosed in the patent.
Q. And the patent discloses the type of precompression pump that should be used -- I don't have my bottle, but the type of bottle that should be used with Nasacort AQ?

A. **All the patent discloses about the pump is that it's a precompression pump, but it gives absolutely no information about the pump and the pump determines a lot about the actual spray that is emitted. It just discloses a precompression pump.**

Q. **We'll hold that point for a moment while my colleagues get me a document on that, but we'll continue on this line.**

With the same assumption that Dr. Berridge's conclusion is correct about deposition of Nasacort AQ in the frontal sinus, the patents in suit tell you what dose of the active to include, tell you that the drug should be given intranasally and it should be given once daily. Is that correct?

A. **I'd appreciate if you could highlight that, but that sounds approximately correct, yes.**

Q. **We could. These are noncontroversial points so I will not bother to highlight them.**

So if Dr. Berridge's conclusion is correct, it's not correct, is it, that a person of ordinary skill in the art wouldn't know where to begin to make such a nasal spray formulation that deposits in the frontal sinus. They would have all the information in the patents at hand, wouldn't they?

A. **Again, if Dr. Berridge's data indicates that**

Nasacort's AQ reaches the frontal sinus, then the patent has sufficient information. But Dr. Berridge didn't study the deposition of Nasacort AQ, he studied the deposition of a radiolabeled position of that formulation.

Q. **Now, was that an issue you expressed in either of your opinions, Dr. Donovan?**

A. **I don't believe it was directly expressed, but it's part of my scientific evaluation of Dr. Berridge's results.**

Q. **So the carbon 11 atom in TAA made a difference? That is what you are telling me now?**

A. **That is what is being measured is the carbon atom in TAA.**

Q. **Now, your opinion on nonenablement is based on you having seen no data that clearly demonstrates that the formulations described in the patent can be retained in the frontal sinus for at least about an hour?**

A. **That's correct, yes.**

Q. **And do you know who bears the burden of proof on the issue of enablement? Is it Aventis or is it Barr? And you may not know.**

A. **I don't specifically know that point of law, no.**

Q. **That's fair. That's fair.**

MR. BERGHOFF: Let's go to -- and I'm just picking up the point I passed over before about the patent not telling us anything about the pump. Let's go to Column

10, Line 28 of PTX-1.

BY MR. BERGHOFF:

Q. This is the '573 patent. Do you have that in front of you, Dr. Donovan?

A. Yes, I do have the patent in front of me.

Q. And, in fact, the patent tells us that the bottle containing the nasal formulation is capped with a metering pump and that the pump is a Valois, VP7/100S pump with a dip tube, an actuator, an overcap and a safety clip. Do you see that?

A. I see that, yes.

Q. So you weren't correct that the patent doesn't tell us anything about the pump?

A. Well, in the example, it tells which pump was used, but I don't know enough about the Valois VP7/100S to know what factors it had regarding the final deposition of the formulation contained within. But in the example, it does specify which pump they preferred, apparently.

Q. And you are, as I recall from your testimony, one of 10 people in the world who specializes in nasal spray formulation and you are not familiar with this particular pump or its performance characteristics?

A. Again, this is a device. The pump is the device part of the nasal delivery system. I specialize in formulation development. I'm aware of issues with the delivery devices

but I don't specialize in the types of delivery devices and their particular specifications.

Q. Well, the particular delivery device used is very important, is it not?

A. Yes, it is.

Q. How the product deposits within the nose?

A. Yes, it is.

Q. And you have no expertise on that to bring to this courtroom?

A. Well, I have expertise in how important the device is, but I don't develop those devices and I don't know all of the information about their characteristics as devices.

Q. And you are unfamiliar with this particular pump?

A. Again, I know the Valois VP7. I could not begin to tell you anything about the pump specifications about it off the top of my head, but I'm certainly aware it is a commonly used pump system.

MR. BERGHOFF: No more questions, Your Honor. Thank you.

THE COURT: All right. Redirect, counsel.

MR. HURST: Very briefly.

REDIRECT EXAMINATION

BY MR. HURST:

Q. Dr. Donovan, as long as we're engaging in hypotheticals, if we were to assume that Dr. Berridge's data

was right and that the Nasacort AQ reaches the frontal sinus -- by the way, you don't agree with that hypothetical, do you?

A. No, I don't.

Q. But just assume in this world that nasal sprays can reach the frontal sinus. If it was true for Nasacort AQ, can you think of any reason why it wouldn't also be true for Beconase and Flonase and Vancenase and other prior art nasal sprays?

A. Well, if it's true there is something about being able to reach the frontal sinus that I don't understand, then it's very likely that other formulations can access a pathway that I don't understand.

Q. And does Nasacort AQ -- I used the term Nasal Spray 101 in opening. Does the patent teach you anything special about how to make nasal sprays that wasn't already known in the prior art?

A. No, it uses the exact same components that were used by other products containing steroids as nasal sprays.

MR. HURST: Thank you, Dr. Donovan.

THE COURT: Thank you, doctor.

THE WITNESS: Thank you.

THE COURT: Your next witness, counsel.

MS. RURKA: The defendants would like to call Dr. Barry Siegel to the stand.

THE COURT: All right.

- - -

DEFENDANT'S TESTIMONY

... DR. BARRY A. SIEGEL, having been placed under oath at 4:19 p.m. as a witness, was examined and testified as follows ....

- - -

MS. RURKA: Your Honor, may I approach the witness?

THE COURT: Yes.

MR. HURST:

DIRECT EXAMINATION

BY MS. RURKA:

Q. **Good afternoon, Dr. Siegel.**

A. **Good afternoon.**

Q. **Could you please state your name for the record?**

A. **My name is Dr. Barry Allen Siegel.**

Q. **And what is your area of expertise, Dr. Siegel?**

A. **I'm a physician; and my specialty is in Radiology and Nuclear Medicine.**

Q. **And what sort of -- do you do positron emission tomography testing?**

A. **Yes, absolutely.**

Q. **Of the kind performed by Dr. Berridge?**

A. **Well, positron emission tomography. I have not done**

the specific types of tests that Dr. Berridge performed but it's the same basic technique.

Q. Before we get to your opinions in this case, could you please describe your educational background for the Court?

A. Yes, very easily. Basically, I've been at Washington University for essentially my entire career. I started there as an undergraduate in 1962.

I then went on to medical school, from which I graduated in 1969.

I did my medical internship, followed by a training program in Radiology and Nuclear Medicine.

At which point in 1973, I joined the faculty of the Department of Radiology as the Director of Nuclear Medicine and, except for a brief little under two-year stint in the Air Force, have remained at Washington University.

Q. So you're a board certified physician?

A. I am.

Q. And what boards are you certified by?

A. I'm certified in Nuclear Medicine Diagnostic Radiology and the radiology subspecialty known as Nuclear Radiology.

Q. How long have you been involved in PET testing?

A. Approximately 30 years. PET, as I think we may have heard yesterday, was actually invented in its modern form at

Washington University by colleagues in my department, and it was happening while I was a resident and when I first became a member of the faculty. So I watched the early evolution of PET. My own first involvement with PET from a research point of view was the study that was done in 1976, published in 1977. So about 30 years.

Q. **So is Washington University well known for positron emission tomography testing?**

A. **Unequivocally, I think Washington University is considered one of the centers of PET research in the world. We have been an extremely well funded radiology department for the last several years. We've had the highest level of NIH funding of any department in the country and a substantial majority of our funding is related to PET.**

Q. **Dr. Siegel, what is your specialty in PET?**

A. **My specific area of expertise in PET relates to the use of PET in cancer for diagnosis staging, restaging and treatment assessment of tumors, developing new radiopharmaceutical probes for evaluating tumors, but I am broadly familiar with all aspects of PET.**

Q. **How are you broadly familiar with PET?**

A. **Well, aside from the fact that I perform PET of other parts of the body on a clinical basis, I'm also very heavily involved in the review of PET research in our institution.**

I've been chairman of our radioactive drug

research committee since it was formed in 1980. And this committee, which is an FDA-approved committee, is responsible for reviewing all of the PET research performed at the institution.

So I would say that over the years, I've reviewed 300-to-400 research protocols involving PET and determined that the science was valid and that the studies were going to be safe and could proceed; and that research has covered the full spectrum of the applications of PET, including cardiac, neurology, oncology and drug development.

Q. **Are you a published author?**

A. **I am, indeed.**

Q. **Do you publish in PET?**

A. **I do.**

Q. **How many articles have you published in PET?**

A. **About 120 of my total of about 320 publications.**

Q. **Have you had any experience with editing scientific journals?**

A. **I have. Over the years, a number, but I'm currently either an assistant editor or associate editor or on the editorial board of about six journals. And, specifically, perhaps relevant to this case, I'm an associate editor of the Journal of Nuclear Medicine.**

Q. **And that's the journal in which Dr. Berridge's 1996 study was published?**

A. **That's correct.**

MS. RURKA: Your Honor, I'd like to proffer Dr. Siegel as an expert witness in the area of positron emission topography.

THE COURT: Any objection?

MS. BALDWIN: I have no objection.

THE COURT: He is accepted as an expert in that field.

BY MS. RURKA:

Q. **Were you asked to conduct some analyses by the attorneys for Barr in this case?**

A. **I was.**

Q. **What were you asked to do?**

A. **I was asked to review the studies that were performed by Dr. Berridge, to evaluate the distribution in kinetics of radioactively-labeled steroids in the nasal cavity and then to express some opinions about my reviews.**

Q. **What do you mean by "distribution in kinetics?"**

A. **Well, the studies were designed to evaluate where radiolabeled triamcinolone acetonide, TAA, Nasacort AQ was located in the nasal cavity and then also how rapidly, once the drug was deposited, it cleared from various regions in the nasal cavity. And, similarly, the later studies looked at radiolabeled Flonase.**

Q. **Did you reach an opinion based on your analysis of**

these studies by Dr. Berridge?
A. I did.
Q. What are your opinions?
A. Well, my two principal opinions are that there was no significant difference in the way that Flonase and Nasacort AQ were deposited in the various regions of the nasal cavity and were cleared from the nasal cavity. And, in addition, my opinion was, is that there is no scientific evidence to support the notion that Nasacort AQ was deposited in the frontal sinus.
Q. You didn't review any PET studies that were done on Barr's ANDA product. Correct?
A. I did not.
Q. Okay. And you heard Dr. Berridge testify yesterday about his opinion about Nasacort AQ depositing in the frontal sinus?
A. I did.
Q. Do you agree with him?
A. I do not agree with Dr. Berridge.
Q. Why don't we discuss how Dr. Berridge conducted his studies. I know the court has heard some of this yesterday, but can you give us an overview of how the studies were conducted?
THE WITNESS: It's late in the day, Your Honor, and I'll try to paint this with a very broad brush.

THE COURT: Okay.

THE WITNESS: Very simply. As I think you've heard, the drug is labeled with a radioactive tracer, either carbon 11 in the case of Nasacort AQ or fluorine 18 in the case of Flonase. It is then put into the pump along with some of the stable drug. It's sprayed into the nose. The subject then goes into the PET scanner for a fairly complicated procedure. But from a simplest point of view, a series of images are required over about 90 minutes to two hours, depending on the study. And then when all of that is completed, or sometimes before, the subject has a magnetic imaging scan that is done to look at the anatomy, and then the two data sets are put together, they're fused, registered, aligned, choose your word that you like best, and that information is then analyzed using regions of interest to try to assess where the drug deposits and how quickly it clears from those regions of deposition.

Q. **Why would you have to register the PET images with the MRI images?**

A. **Well, you need the magnetic resonance imaging image to provide the anatomic information about where the drug is located. Basically, the PET image -- and I think we saw an example of that yesterday -- is a blob of radioactivity sitting in the middle of the face in the nasal cavity, and there are really no anatomical clues on that image. So it's**

absolutely necessary to register or fuse the PET data with the magnetic resonance data so you can say oh, yes, I see that part of the blob is in the frontal cavity. This part of the blob is in the turbinate region.

Q. Okay. Did you prepare a demonstrative exhibit to show how these three studies were conducted?

A. I did.

MS. RURKA: Can we pull up Demonstrative 43? Your Honor, I'm sure you have seen this enough times.

THE WITNESS: In fact, Your Honor, I was going to ask you questions about the anatomy.

THE COURT: I'm ready for your test.

(Laughter.)

BY MS. RURKA:

Q. Were all three studies conducted in the same manner?

A. No, there is at least one very important different difference between the three studies.

Q. What is the difference?

A. Well, the key difference I believe is that in the 1996 study, Dr. Berridge used a cubicle array in order to develop his regions of interest for measurement of the activity in each region whereas in the 1998 and the 2002 study, he had more sophisticated software available to him and now he was able to use contoured regions of interest

that conformed to each anatomical structure from which he wished to measure activity.

Q. So how do you draw regions of interest? Can you describe the contoured regions of interest first?

A. Sure. I can try. If you see now this green outline that has come up -- my laser pointer is just passable here. But this green outline shows a contoured region placed on the frontal sinus and the investigator or the technologist would basically be working at the computer and following the borders seen on the MRI scan to place the region of interest over the frontal sinus so that we can measure all the activity within the frontal sinus.

Q. You said you used the cubic regions of interest in 1996. Could you please describe that?

A. Sure. If we could have the next.

So this is an example, for purposes of illustration, of cubes. By Dr. Berridge's report, these cubes were about .7 inches on a side, 1.8 centimeters overlay over the entire volume where the radioactivity was. Here, we're looking at the cubic array only in a single plane. And each cube, in order to make the measurement, the investigators needed to assign the cube to a particular anatomical region.

Q. So is that a more or less accurate way of assigning regions of interest to determine exactly where the drug

goes?

A. Well, I think it's an inherently less accurate way of making the measurement, and for the simple reason that the anatomical structures we're trying to assess are not cubes. They have curved borders rather than straight borders and, therefore, it's reasonably likely to assume there will be some overlap from one cube, from one region to an adjacent region. I think we can illustrate that.

Q. Yes. Could you illustrate the overlap, please? Let's look at the frontal side.

A. So if we look here, you can see there are four cubes that include part of the frontal sinus. Now, this shows all four of those cubes filled in but notably the lower right cube also includes a tiny little fraction of the upper nasal cavity.

Q. And so what would that mean if you assigned that cube to the frontal sinus?

A. So if you assign this cube to the frontal sinus, then some of the activity in the frontal cavity, which we know is a region that has a lot of the radioactive tracer, would be incorrectly assigned to the frontal sinus.

Q. And that would mean there was deposit, you were registering deposit in the frontal sinus that was not in fact there. Is that right?

A. That's correct.

THE COURT: Remember, this is your witness, counsel.

MS. RURKA: Sorry, Your Honor.

Q. **You heard Dr. Berridge testify yesterday that overlapping cubes would, if he reached -- if he had a situation like this, where he a cube that overlapped at the frontal sinus and part of the upper nasal cavity, that he would assign that to the upper nasal cavity rather than the frontal sinus. Right?**

A. **I did hear him say that.**

Q. **Do you agree with Dr. Berridge that that is what happened?**

A. **The truth of the matter is, I don't know. These PET data no longer exist. There are no source documents kept as a result of these experiments that show how the regions of interest were actually assigned, something that I routinely do in my own research when I am assigning regions of interest. I maintain a separate source document of the regions. So I don't know whether he actually would have taken this cube and assigned it to the frontal cavity.**

Q. **Did you review Dr. Berridge's publication in the Journal of Nuclear Medicine, the 1996 study?**

A. **I did.**

Q. **Was there anything reported in that publication about how he assigned the cubic regions of interest?**

A. **Only that the cubic regions were assigned to anatomical regions, but no mention about how assignment was made when a particular cube seemed to overlap from one region to another.**

Q. **And did he report anything about a potential for understating the deposition in the frontal sinus based on this assignment of cubic regions of interest?**

A. **He did not.**

Q. **As a scientist would you report these data without addressing the assignment of the regions of interest?**

A. **I don't think I would. And for a couple of reasons. First of all, I think it's important to have your methodology described as accurately as possible. Journals sometimes impose limitations on the number of words you can use. But there was no limitation on the number of words Dr. Berridge could have used in his study or report that he provided to the Aventis precursor, RPR.**

But importantly, Dr. Berridge also in the article in the Journal of Nuclear Medicine comments that unexpectedly, we found activity in the frontal sinus. To wit, we have discovered something that we didn't expect would occur, and therefore, I think as a scientist it was incumbent on him to explain that he took great care to make sure that that measurement was not an artifact of the measurement technique but, in fact, represented activity in

the frontal sinus.

Q. And you reviewed the 1996 final study report as part of your analysis in this case, did you?

A. I did.

Q. And did you see anything in that study report that described Dr. Berridge's testimony yesterday about how he assigned the frontal sinus regions of interest?

A. I did not. And I looked many times to try to find the sources.

Q. Are there any other potential sources of error for positron emission product testing that might cause periods of radioactivity in a region where it was in fact not?

A. There are.

Q. What are those?

A. I think we have a demonstrative that will help with this, maybe.

Q. Can you pull up Demonstrative 45?

A. This is simply a list. What we have already talked about is overlapping regions. In addition, even if the regions don't overlap, there is a problem that Dr. Berridge mentioned, known as spillover. There is another problem known as scattered radiation. And then there is the third problem of misalignment of the PET image with the magnetic resonance imaging.

Q. Can spillover be corrected?

A. **Spillover is really a fundamental limitation of the PET scanner itself because of its resolution limits, and all one can do to address spillover where you define the borders of your regions, which you can't correct for.**

Q. **Can scatter be corrected?**

A. **There are scatter corrections that can be used in PET images. It's not entirely clear to me whether Dr. Berridge used or did not use scatter corrections in these particular studies. Scatter, however, provide uniform background -- the scatter correction subtracts a uniform background from the PET image.**

And if you have a very hot region and not far away, a region with essentially no activity in it, the scanner correction will not correct for the fact that there will be scanner into that cold region. Sorry for that complicated explanation.

Q. **And for a region like the frontal cavity that is hot, would the scatter, would you expect the scatter to be fully corrected if it is adjacent to the frontal sinus?**

A. **No, I would not expect it to be, even if a scatter correction were applied.**

Q. **Okay. The last one on the demonstrative.**

Is misalignment, can you just explain what misalignment is?

A. **Well, misalignment would be when, even though we**

think the PET image is aligned with the MRI image, it is, in fact, not aligned. Although we think that this might be a relatively straightforward thing to do, in actual fact, Dr. Berridge designed a very complicated experiment, albeit an elegant one, in which, by my count, there were at least five separate steps of image alignment that were necessary in order to get these images lined up all the way through the data sequence, and that's even if we discount the possibility that there was patient motion at some point during the procedure, and we know that there was some motion as well that had to be corrected.

Every time one would undertake one of these alignment steps, some of which were computer-aided, but some of which were done manually, there is the possibility to introduce human error into the alignment.

Q. Dr. Siegel, let's talk briefly about the three studies that Dr. Berridge performed. The 2002 study, if you could pull up Defendant's Exhibit 5, at Page 10, the first two lines.

Did you hear Dr. Berridge testify yesterday about the due to unusual variations between observations from individual subjects, his testimony that that informed -- that that testimony described the data as being bad from this study?

A. I heard him say that yesterday.

Q. **Is there anything in this the 2002 study report that actually suggests to you as a scientist that there is bad data that were generated by this study?**

A. **No. I see the sentence about unusual variation from subject to subject. But that could be due to biologic variability. I did not see anything else in the report that led me to believe that Dr. Berridge said, discount the results of this study because the study was flawed.**

Q. **And Dr. Berridge also -- did you see any unusual variation in the frontal sinus data in this study?**

A. **No. There was no unusual variation in the frontal sinus measurements with both Nasacort AQ and Flonase in this study. Both were zero.**

Q. **If you could pull up Page 12?**

THE COURT: I think she meant Dr. Siegel.

MS. RURKA: Did I say Dr. Berridge?

THE COURT: That's okay.

BY MS. RURKA:

Q. **I apologize, Dr. Siegel.**

And this shows the results that Dr. Berridge -- did these show the results that Dr. Berridge achieved?

A. **Yes, these are Dr. Berridge's results and conclusions that there was no uptake observed in the frontal sinus. And as you can see, there was Nasacort AQ, the reported value is 0.00, on average during initial distribution.**

Q. **Dr. Siegel, did you analyze the data from the 2002 study report in any fashion?**

A. **I did. I prepared a graphical display just to show this more clearly.**

Q. **Could you pull up -- this is Demonstrative Exhibit 40. What is this graph?**

A. **So this is a graph, the upper graph is what we have got labeled here as the average of the nasal cavity. I think we have also heard this referred to as the frontal cavity and also heard it referred to as the vestibule. So choose your term. But it's showing the percent of administered dose versus time out to about, I think this is 80 minutes with about 60 percent initially deposited and then slowly clearing in that space.**

Then in the frontal sinus, we can see that basically the average result across time is zero percent.

Q. **Why did you use the frontal cavity -- or the nasal cavity as it is labeled here and the frontal sinus to compare?**

A. **Because I thought that the frontal cavity would be the region that would most likely be causing a problem with a frontal sinus measurement if there was overlap, spillover, or scatter, or misalignment, for that matter.**

Q. **Did you review the 1998 study data?**

A. **I did.**

Q. **What did you review from the 1998 study?**

A. **Well, we did not have a complete final report for the 1998 study. And as I have already mentioned, we don't have any raw PET data left for any of these studies. What I had was a poster that was presented at a meeting from the 1998 study results -- Dr. Berridge showed that poster yesterday -- and a spread sheet of data, which were the processed results from that study.**

Q. **And I think Dr. Berridge, did you hear Dr. Berridge testify yesterday about the most -- I think he testified that only three of the subjects acquired any frontal sinus uptake out of the five subjects that were studied?**

A. **I believe that's what he said.**

Q. **Okay. Did you hear him testify that one of those subjects had .5 in the frontal sinus, .5 percent, one of the subjects, and both of the other subjects had less than .2 percent?**

A. **I believe that's what he said and what his graph showed.**

Q. **Did you do anything to analyze the data in the 1998 study?**

A. **I did, using the spread sheet data available to me I prepared a similar plot.**

Q. **And this is Demonstrative Exhibit 39. What does this graph show?**

A. **Essentially the same thing for the 1998 study. The upper graph is the average of the nasal cavity, or the frontal cavity, and the lower graph is the frontal sinus, and once again, about 50 to 60 percent getting initially into the nasal cavity and essentially zero percent throughout the time of, the period of measurement on average in the frontal sinus.**

Q. **If you compare these two graphs, what do you see, the 1998 graph and the 2002 graph?**

A. **They look very similar, if we put them side by side, I think you can see them here, despite the interruption in the curves here, which is the way Excel plotted them, the shapes of the curves are quite similar and the frontal sinus curves are both zero.**

Q. **So, in your opinion, Dr. Siegel, did the 1998 study show deposition of TAA on the frontal sinus?**

A. **I don't think so.**

Q. **For Dr. Berridge's numbers that he reported yesterday, or he testified to yesterday, do you think there is anything else that could be responsible for those low numbers of frontal sinus deposit?**

A. **The values of about .5 and less than .2 in three of the five subjects. Yeah, I think all of the factors that I have already talked about could be contributing. We don't really have the raw data of the regions of interest to see**

whether there was the possibility of spillover, whether there was a possibility of any degree of overlap, despite the contoured regions or whether scatter could be contributing. But I think given how low those results are that it seems to me that that is far more likely than actual deposition in the frontal sinus.

Q. And of the three studies, the 1996 study, the 1998 study and the 2002 study, which do you view as the most suspect with regard to frontal sinus deposit?

A. I view the 1996 study as most suspect. The values reported in the frontal sinus are much, much higher. They are clearly outliers by comparison with the two subsequent studies, and the cubic regions of interest, I think, represent a fundamentally imperfect measurement technique, the limitation of the 1996 study nonetheless, but I think still a flaw.

Q. As a scientist, Dr. Siegel, if you had achieved the results in the 1998 study and the 2002 study that Dr. Berridge achieved, after you had published results from the 1996 study, would you do anything to correct or to address the disparity in results between the three studies?

A. Yes, I think I would have. I have now made a scientific publication that has told the world that something quite unexpected has happened, the tracer, the drug has gotten into the frontal sinus. I now have two

subsequent studies that say, hmm, maybe that is not really what's going on. And I would have done one of three things. I would have gone back to the 1996 study, and reanalyzed the data with the now improved software available to me so that I could use the contoured regions of interest. Or I would have gone to the sponsor and say, we have got some data here that don't jibe across three studies, we should do some additional study, very carefully controlling whatever potential sources of error we might think might have been involved in these studies, as we look back upon how they were performed.

Or, if I thought that the '98 and the 2002 study results made sense, I might at least write a letter to the editor of the Journal of Nuclear Medicine saying, more recent data calls into question our report of this unique, unexpected finding of drug entry into the frontal sinus.

Q. Would that require a full manuscript?

A. No, it wouldn't. A letter to the editor describing subsequent data would certainly be accepted by virtually any journal as a core addendum.

Q. Having reviewed all the data on frontal sinus deposit from Dr. Berridge's PET studies, what is your opinion about whether or not name Nasacort AQ deposits on the frontal sinus?

A. My opinion is that the substantial majority of the

scientific evidence indicates that Nasacort AQ does not deposit on the frontal sinus.

Q. You mentioned one other opinion that you had expressed in this case regarding deposition and retention patterns for Nasacort AQ and Flonase?

A. Correct.

Q. Your Honor, this is related to the secondary considerations of nonobviousness case that plaintiffs are going to put forth later in the trial.

So you were asked -- where does Flonase deposit for purposes of this case?

A. For purposes of this case, as I understand it, Flonase deposits in the frontal cavity or nasal cavity, in the turbinates, and in the maxillary sinuses.

Q. Just like Nasacort AQ?

A. Just like Nasacort AQ.

Q. In the 2002 study report, Dr. Berridge discusses deposition patterns of Flonase and Nasacort AQ, comparative deposition of those two products. Is that right?

A. That is correct.

Q. Did you review the portion of his study report?

A. Yes, I did.

Q. What did he conclude?

A. He concluded that there was no statistically significant difference in those deposition patterns.

Q. **Could you pull up demonstrative -- DX-5, please. 2002 study report.**

This is the first sentence, he says, the observed -- the study showed several trends in the data, but due to unusual variations between observations from individual subjects, the observed differences did not reach statistical significance.

A. **That's correct.**

Q. **He was concluding that deposition pattern, the deposition pattern between the two products would not be statistically significantly different?**

A. **That's correct. Or was not statistically significantly different.**

Q. **If you pull up Page 12, here is a portion where he is talking about initial distribution average results. What was his conclusion regarding the initial distribution of Nasacort AQ and Flonase?**

A. **Well, as you can see highlighted here, he said that most regions showed quantitative deposition that was very similar between the two formulations to the extent that the difference would be unlikely to be functionally detectable.**

Q. **What is your understanding of what he means by that functionally detectable?**

A. **To be quite honest, I am not absolutely certain, but in my interpretation of that phrase, it is that these**

differences in drug deposition would not likely relate in any way to the safety or effectiveness of these products for their approved indications.

Q. Did Dr. Berridge also reach conclusions about the clearance rate of Flonase versus Nasacort AQ?

A. He did.

Q. Could you pull up Page 10 again. What did Dr. Berridge conclude about the clearance rates?

A. Okay, as you can see here in yellow, also, the clearance rates of both formulations seem to vary during the course of the experiment with no clear difference being noted.

In some subjects, an apparent better retention of Nasacort AQ was noted. However, others seemed to show the reverse. The concentration on target tissues towards the end of the observation period were more similar than the initially deposited concentrations.

Q. This 2002 study, how many subjects participated?

A. There were six subjects who participated in the study.

Q. And what were the subjects administered?

A. They were administered carbon 11 labeled triamcinolone acetamine and fluorine 18 labeled fluticasone propionate.

Q. What was the design of the study?

A. **The design was a fairly standard randomized controlled crossover design, they have an equal distribution of genders, as I recall, in the study. And the randomized method indicated decided which of the two drugs was given first.**

Q. **I am sorry. Does randomized -- what does randomized mean actually?**

A. **Randomized means in this study that the drug that was going to be given first to a given subject was determined by random selection.**

Q. **So different subjects got different drugs?**

A. **As the first drug.**

Q. **As the first drug?**

A. **Correct.**

Q. **And when were the drugs, what was the difference in time between when the two drugs were administered to each subject?**

A. **My recollection in this study was that they were either one day and the next day, but most of them were within a couple or three days of each other, and the MRI was also performed within that same time frame.**

Q. **Okay. Let's move to the 1998 study briefly. How about the 1998 study, what was the study design in that one?**

A. **The 1998 study was originally a study designed just to look at the distribution of Flonase. After that portion**

of the study had been completed, the investigators amended the clinical protocol and then decided to do a crossover comparison, if you will, with Nasacort AQ, and they did that on times ranging from three to six months after the original studies were performed with Flonase.

Q. So when did the subjects first come in for the 1998 study to be administered Flonase?

A. The dates and years, do you want that?

Q. Yes. If you can remember.

A. I think they were, I am going to get this wrong, but they were running up to about December of 1997, as I recall.

Q. And when were they administered, generally administered, the Nasacort AQ?

A. In the May time frame. I think it was like December through February and then extending up to the May time frame.

Q. So did you see any, prior to this litigation, was there any statistical analysis produced, that, was there any statistical analysis done prior to this litigation that was produced to you to review?

A. For the 1998 study.

Q. For the 1998 study?

A. There was not. The poster did not contain any statistical analysis of the results.

Q. Did you see any since the litigation began, any

statistical analysis, I should say, of the 1998 study?
A. I did.
Q. What was that analysis?
A. Okay. In Dr. Berridge's rebuttal report, after he had reviewed my expert report, he went and analyzed the data from the 1998 study, I believe, for seven regions, comparing Flonase and Nasacort and shearing.
Q. Could you pull up DX-358 at Page 28. Are these the results you are discussing?
A. That's correct.
Q. Can you just, the statistics are very difficult, could you just explain briefly what this chart is showing?
A. Sure. So on the left-hand column we have the time of the observation, and above we have each of these seven regions, that I hope we can read. What the table is actually including is a P value, a statistical significance value, if you will, for the comparison of Flonase versus Nasacort in the six subjects who got Flonase and the five who got Nasacort, in that region at that point in time. So we have a table with multiple comparisons, where the table entries are blank, the result was not considered to be statistically significant, and where the value was said to be extremely highly statistically significant, Dr. Berridge has entered 0.0000. Otherwise, the numbers represent the P values.

Q. **So what would a significant finding be? What would the number be for it to be a significant finding?**

A. **So in a traditional test like this, a T test, which is what this is, an un-paired T test, where you are comparing one set of observations with another set of observations, as a single comparison, you would use a cutoff P value of less than 0.05, and what that means is you are setting the threshold so that you won't reach a false conclusion due to chance alone more than one time out of 20.**

Q. **So if its below .05, what does that mean?**

A. **It means that you conclude based on your statistical inference assumptions that the changes are not likely due to chance alone, and in fact represent a statistically significant difference in those two sets of measurements.**

Q. **Did you attempt to replicate any of Dr. Berridge's analysis here?**

A. **I did.**

Q. **Can we pull up Demonstrative 38, please. What did you do here?**

A. **Okay. The first thing I did when I saw this report is I looked at the P values, and then I went back and looked at the spread sheet and looked at the raw data, the values he had measured in these regions, and said, this just can't be. The standard deviations and the means for these different regions just can't be this statistically**

significantly different.

What I simply did was took a random sample of four of the measurements in the inferior turbinate, that just happened to be the first column, I picked them at random so that the P values that Dr. Berridge calculated covered a wide range of P values, and then I recalculated them myself using a well-documented program for doing an unpaired T test that's available readily on the web. And I found that none of those four measurements were statistically significant.

Q. Is that because they are all above .05?

A. That's correct.

Q. Is .05 the correct cutoff for data like these?

A. No, that is an additional problem. So .05 is the cutoff that you use when you are doing one comparison, one set of data versus another set of data. When you have a big table of data, where you are about to do multiple comparisons, then statisticians tell us that what we need to do is to correct for the fact that when we do multiple comparisons, we are more likely to get false results, and we do a correction. And the most commonly performed correction is something known as the Bonferoni (phonetic) correction, and that is what I believe Dr. Berridge sort of applied to his analysis.

THE COURT: Counsel, I am going to have to cut

you off. I have a judges' meeting at 5:00. Was it your plan to have Dr. Siegel remain over until tomorrow or was he returning?

MS. RURKA: If we could have him remain over, I probably have just a few more minutes with him tomorrow.

THE COURT: How long do you think your cross will take, counsel?

MS. BALDWIN: You will probably want to go to your judges' meeting.

THE COURT: I am thinking, my meeting probably is not going to take that long. If the Doctor had a flight out, I was considering coming back. If that's not the case and he is going to be here anyway, he is going to be here anyway.

MS. RURKA: He is going to be here.

THE COURT: Fine. We will recess.

(Court recessed at 5:00 p.m.)

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Reporters: Kevin Maurer and Brian Gaffigan